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# Development of a Physiologically-Based Pharmacokinetic Model of Trichloroethylene and Its Metabolites for Use in Risk Assessment


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Human Effectiveness Directorate
Biosciences and Protection Division
Applied Biotechnology Branch
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## NOTICE



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**THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.**

**FOR THE DIRECTOR**

//signed//

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A physiologically based pharmacokinetic (PBPK) model was developed which provides a comprehensive description of the kinetics of trichloroethylene (TCE) and its metabolites, trichloroethanol (TCOH), and trichloroacetic acid (TCA), in the mouse, rat, and human, for both oral and inhalation exposure. The model includes descriptions of the three principal target tissues for cancer identified in animal bioassays: liver, lung, and kidney. Dose metrics that can be calculated with the model for cancer risk assessment include the area under the concentration curve (AUC) for TCA in the plasma or liver, the peak concentration and AUC for chloral (CHL) in the tracheo-bronchial region of the lung, and the production of a thioacetylating intermediate from dichlorovinylcysteine (DCVC) in the kidney. Additional dose metrics that can be calculated for noncancer risk assessment include the peak concentrations and AUCs for TCE and TCOH in the blood, as well as the total metabolism of TCE divided by the body weight. There is currently no adequate data available with which to confidently parameterize a description for another metabolite of interest, dichloroacetic acid (DCA). Model predictions of TCE, TCA, and TCOH concentrations in rodents and humans are consistent with a variety of experimental data, suggesting that the model should provide a useful basis for evaluating cross-species differences in pharmacokinetics for these chemicals. In the case of the lung and kidney target tissues, however, only limited data are available for establishing cross-species pharmacokinetics. As a result, PBPK model calculations for these dose metrics are highly uncertain.

**15. SUBJECT TERMS**
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## PREFACE

The U.S. Air Force (USAF) and the U.S. Environmental Protection Agency (USEPA) jointly sponsored a scientific workgroup to develop a harmonized PBPK model for TCE and its metabolites based on the full range of available science and data. This workgroup was composed of scientists from the USAF and EPA, with technical expertise from Toxicology Excellence for Risk Assessment (TERA) and other scientists under contract to the USAF. The results of this joint USAF-USEPA workgroup served as important input to ongoing TCE risk assessment activities, including a multi-agency consultation with the National Academy of Sciences on TCE science issues. This project was sponsored by AFIOH/RSRE with Brian Howard serving as the Air Force program manager.

Work was conducted under Department of the Air Force Contract No F33615-00-C-6060 and subcontracts to ENVIRON and the University of Georgia. Dr. David R. Mattie served as the Contract Technical Monitor for the U.S. Air Force, Air Force Research Laboratory, Applied Biotechnology Branch (AFRL/HEPB, Wright-Patterson AFB, OH) and Dr. Darol Dodd served as Program Manager for the ManTech/GEO-CENTERS Joint Venture Contract (F33615-00-C-6060).

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## ABBREVIATIONS

| | |
|---|---|
| ACSL | Advanced Continuous Simulation Language |
| ADH | Alcohol Dehydrogenase |
| AUC | Area Under the Concentration Curve |
| BSA | Body Surface Area |
| CHL | Chloral |
| CV | Coefficients of Variation |
| CYP | Cytochrome P450 |
| DCA | Dichloroacetic Acid |
| DCVC | Dichlorovinylcysteine |
| GSH | Glutathione |
| GST | Glutathione Transferase |
| MCA | Monochloroacetic Acid |
| MFO | Mixed Function Oxidase (P450) |
| PBPK | Physiologically Based Pharmacokinetic |
| TCA | Trichloroacetic Acid |
| TCE | Trichloroethylene |
| TCOH | Trichloroethanol |
| UGT | UDP Glucuronosyl Transferase |

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# DEVELOPMENT OF A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL OF TRICHLOROETHYLENE AND ITS METABOLITES FOR USE IN RISK ASSESSMENT

## INTRODUCTION

Physiologically-based pharmacokinetic (PBPK) modeling is widely held to be a useful methodology for improving the accuracy of chemical risk assessment. The goal of PBPK modeling is to simulate the uptake, distribution, metabolism, and elimination of a chemical in an organism, using as realistic a description of the relevant physiology and biochemistry as is necessary and feasible. For its use in risk assessment, PBPK modeling attempts to describe the relationship between external measures of exposure (e.g., amount administered or concentration in air) and internal measures of biologically-effective dose (e.g., amount metabolized or concentration of an active metabolite in the tissue displaying the toxic response) in both the experimental animal and the human.

The most recent EPA cancer risk estimates for trichloroethylene (TCE) were derived in part using PBPK models. In particular, risks of liver cancer based on tumors in mice were estimated using two different PBPK models, [1, 2] as well as with "calibrated" versions of these two models using re-estimated parameters obtained from Markov chain Monte Carlo analysis.[3, 4] The purpose of the study reported here was to develop a single harmonized PBPK model for TCE that included as complete a description as possible of all of the metabolites and target tissues that may be relevant to the toxicity and carcinogenicity of TCE, and to characterize the accuracy and reliability of the resulting model in providing dosimetry estimates in support of a risk assessment for TCE.

### Requirements for a PBPK Model to Support TCE Risk Assessments

Recent quantitative cancer risk estimates for TCE have been based on animal bioassays, specifically liver and lung tumors in mice and kidney tumors in rats, as well as on human epidemiological studies. In the case of the human studies, PBPK modeling can be used to perform route-to-route extrapolation.

For each of the three rodent target tissues, liver, lung, and kidney, there is evidence that the carcinogenicity of TCE may be associated with one or more of its metabolites: trichloroacetic acid (TCA) and dichloroacetic acid (DCA) in the liver, CHL in the lung, and 1,2-DCVC in the kidney. Thus, to be useful in a comprehensive cancer risk assessment for TCE, a PBPK model should include at least three target tissues: liver, lung, and kidney, along with a description of the kinetics of the metabolites that may play a role in the carcinogenic activity.

Several target tissues have also been identified for the noncancer toxicity of TCE, including the liver, kidney, CNS, immune system, and developing fetus. As in the case of the carcinogenicity of TCE, several of these noncancer endpoints appear to be associated with exposure to the metabolites of TCE rather than to the parent chemical itself. For example, trichloroethanol (TCOH), the major metabolite of TCE, has been suggested to be responsible for the observed neurological effects of chloral hydrate.

## Previous PBPK Modeling of TCE

A number of PBPK models have been developed for TCE. However, most have only been parent chemical models; that is, they provide a pharmacokinetic description of TCE itself, but do not include an explicit description of the pharmacokinetics of any of the metabolites. Therefore, these parent chemical models cannot be used for predicting tissue exposure to specific metabolites.

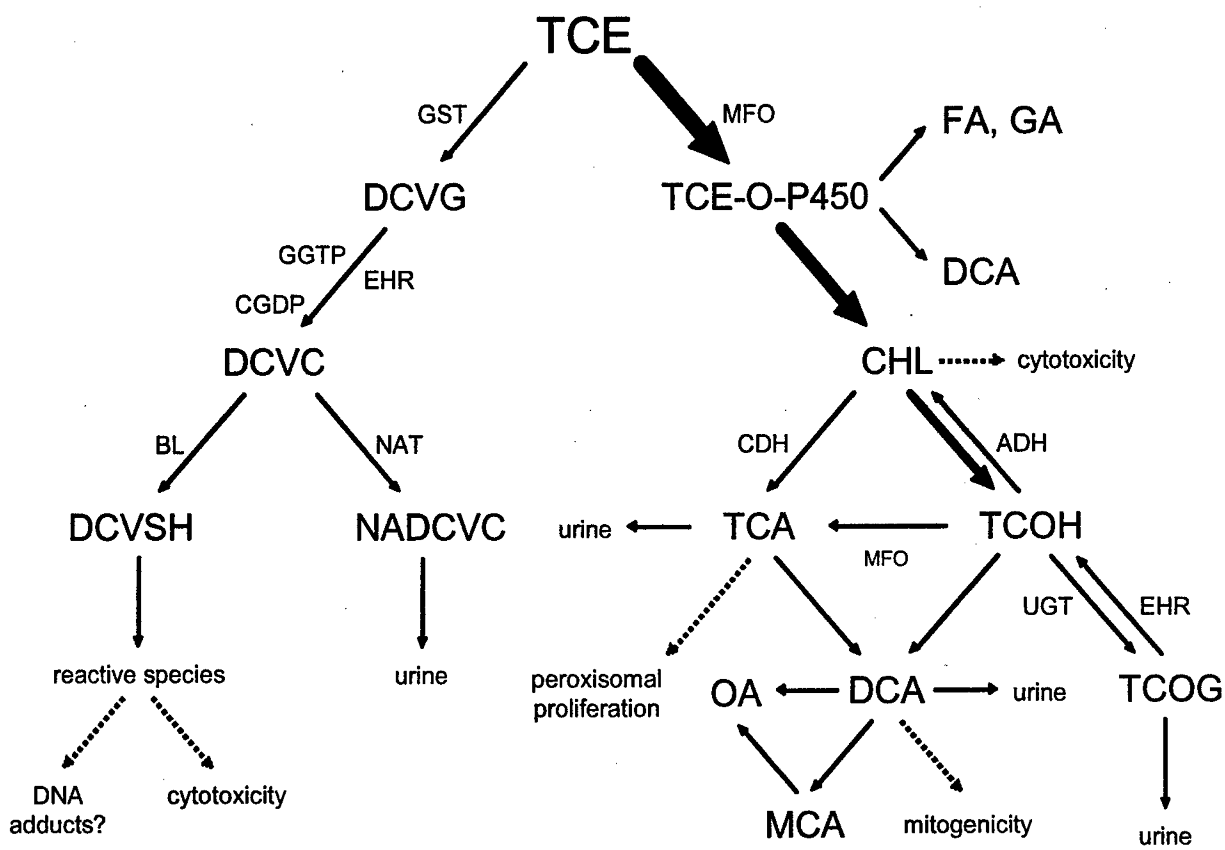
Fisher and coworkers developed a PBPK model for TCE and its principal metabolite, TCA, in the rat and mouse.[5] These rodent models, together with a similar model of TCE and TCA in the human,[6] served as the basis for a PBPK-based risk assessment for TCE liver carcinogenicity[7] based on either average daily total metabolism or average daily AUC for TCA. These models provided the first successful cross-species pharmacokinetic description for a metabolite of TCE. Subsequently, Clewell and co-workers built on the work of Fisher and Allen[7] by adding limited descriptions of additional metabolites (TCOH, DCA, CHL, 1,2-DCVC) and target tissues (lung and kidney).[1] Fisher and colleagues also continued to elaborate and refine their PBPK models for TCE, focusing on the metabolites of interest for liver carcinogenicity.[2] Published models include (1) a model of the kinetics of TCE, CHL, TCA, DCA, and TCOH in the B6C3F1 mouse based on data from corn oil gavage exposures,[8] (2) a model of TCE, TCA, and TCOH in the human based on data from controlled human inhalation exposures,[9] (3) a model of TCE, TCA, and TCOH kinetics in the rat that considers enterohepatic recirculation of TCA and TCOH following oral or intravenous exposure to TCE,[10] and (4) a model of inhaled TCE and its oxidative metabolites in the B6C3F1 mouse.[11] A recent study evaluated various elements of the PBPK description in the rat, including diffusion limited uptake in the fat and liver.[12] Together, these models provide a capability for estimating dose metrics in the mouse, rat, and human in support of a risk assessment for TCE liver carcinogenicity. A potential advantage of these more recent mouse PBPK models[8, 11] is that their calibration includes data on TCA concentrations in the liver. However, since there was no human data on liver concentrations, the human model[9] could not be similarly calibrated. Therefore, the relationship of liver and blood TCA dosimetry must be inferred from data on plasma binding of TCA.[13]

# DESCRIPTION OF THE HARMONIZED PBPK MODEL FOR TCE

## PBPK Model Structure

The structure of a PBPK model is necessarily a function of several variables: the physicochemical and biochemical properties of the compound, the physiological and functional properties of the biological system, and the experimental scenarios being investigated. In addition, the model must incorporate information on the various metabolites generated from the compound that are of importance for the intended application. The metabolism of TCE is summarized in Figure 1, which is adapted from the review by Lash *et al.*[14]

**Figure 1. Metabolism of TCE.** Abbreviations not given in text: (right pathway) CDH: chloral dehydrogenase (aldehyde oxidase); EHR: enterohepatic recirculation; FA: formic acid; GA: glyoxylic acid; OA: oxalic acid; TCE-O-P450: oxygenated TCE-Cytochrome P450 transition state complex; TCOG: TCOH glucuronide; UGT: UDP glucuronosyl transferase; (left pathway) BL: cysteine conjugate β-lyase; CGDP: cysteinyl-glycine dipeptidase; DCVG: dichlorovinyl glutathione; DCVSH: dichlorovinyl mercaptan; GGTP: γ-glutamyl transpeptidase; NADCVC: N-acetyl dichlorovinylcysteine; NAT: N-acetyl transferase.

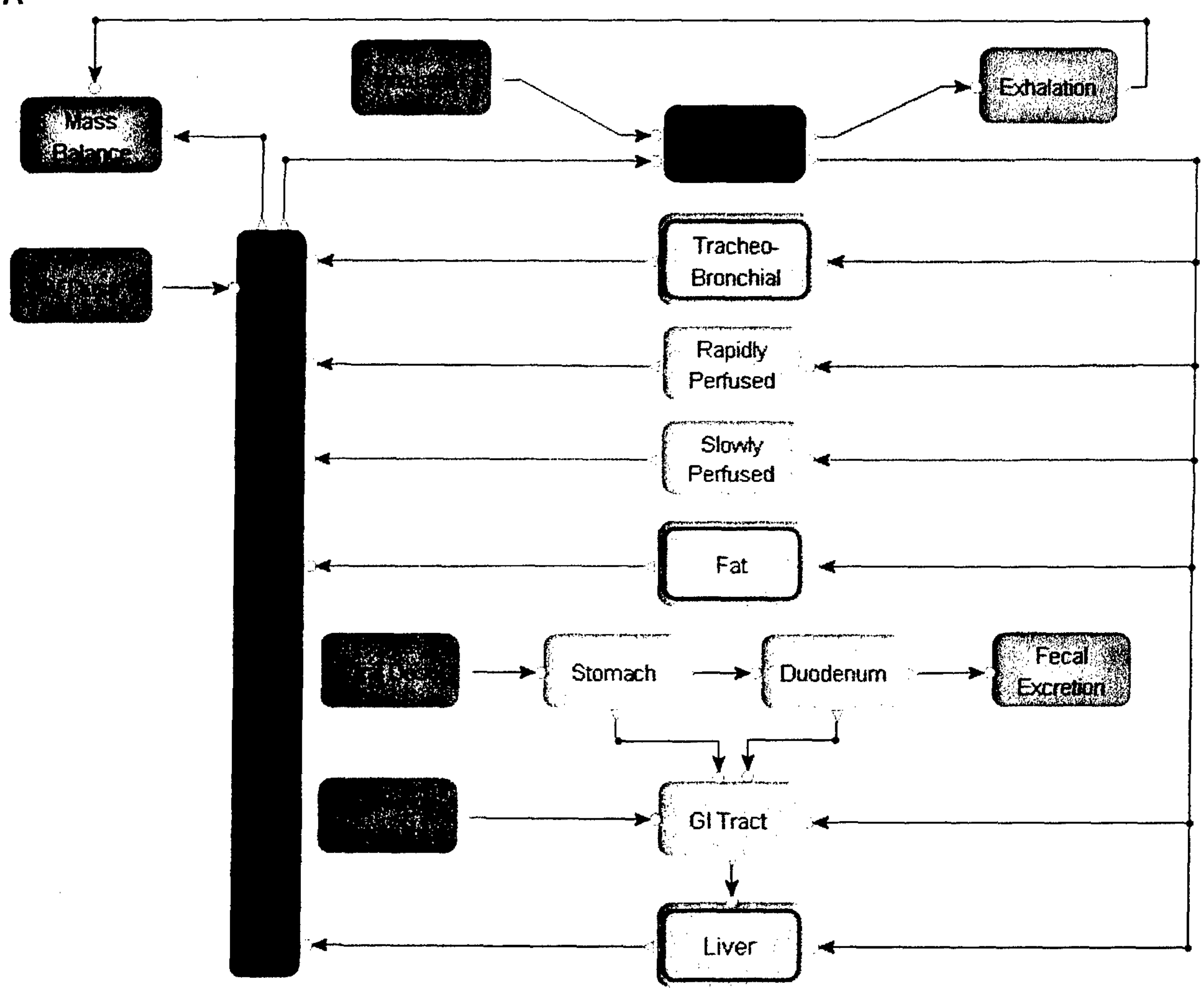



A diagram of the PBPK model developed for TCE and its metabolites is shown in Figures 2 and 3. The model was written in acslXtreme (The AEgis Technologies Group, Inc., Austin, Texas), an implementation of the Advanced Continuous Simulation Language (ACSL). The ACSL source code and command files for the model are included in Appendices A and B, respectively. The parent chemical portion of the model (Figure 2a) includes individual tissue compartments for the liver, GI tract tissue, fat, and tracheo-bronchial region of the lungs. All other tissues are lumped into rapidly perfused (kidney, brain, alveolar region of lungs, etc) and slowly perfused (muscle, skin, etc) compartments. The model has the capability to describe the fat compartment as a diffusion-limited tissue (Figure 2b). The model includes both inhalation and oral routes of exposure. Oral gavage is modeled using a two-compartment description of the gastrointestinal tract in order to better simulate the time course for the uptake of TCE from corn oil gavage. Allometric scaling is used throughout the model (volumes scaled by body weight, flows and metabolic capacities scaled by body weight to the three-quarters power, rate constants scaled by body weight to the negative one-quarter power) to simplify intraspecies and

interspecies extrapolation. Parent chemical dose metrics provided in the model include the concentration of TCE in blood and tissues, as well as the AUC for TCE in the blood.

**Figure 2. Model schematics for the parent chemical.** (A) General model schematic for parent chemical; (B) Sub-model for fat compartment. These diagrams were taken directly from the acslXtreme graphic model display. The blocks are color coded. (Red: blood compartment. Dark Blue: venous blood compartment. Yellow: tissue compartment. Brown: metabolism compartment. Light Green: bile compartment. Dark Green: dosing compartment. Purple: excretion compartment. Light blue: submodel. Rose: mass balance compartment.)

**A**



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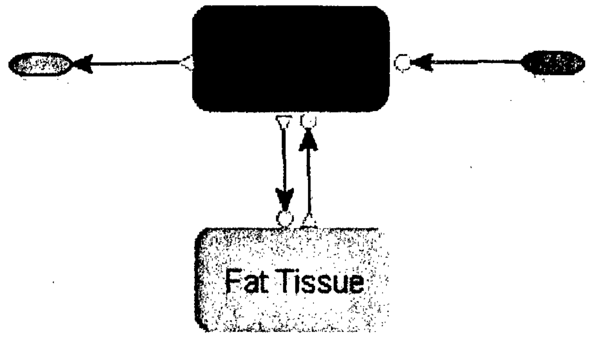



The model includes a number of submodels describing metabolism of TCE as well as downstream metabolism and elimination (Figure 3). These submodels are aimed at providing metabolite dose metrics, including tissue-specific dose metrics for the lung, liver, and kidney target tissues. Except where otherwise noted, Michaelis-Menten kinetics are assumed for all metabolic processes.

Lung Submodel. The tracheo-bronchial region of the lungs, which receives its own arterial blood supply, is described separately to support the modeling of *in situ* metabolism in this region by the Clara cells (Figure 3a). This approach for describing metabolism in the cells lining the airways of the lung was felt to be more biologically accurate than the sequential gas exchange and lung tissue compartments used in the methylene chloride model.[15] However, as long as metabolism in the lung is unimportant for presystemic elimination, as is the case for TCE and methylene chloride, the two descriptions should yield identical results. The dose metrics provided for the lung are the instantaneous concentration and AUC for CHL in the tracheo-bronchial region, which is assumed to be produced by saturable production and clearance of CHL in Clara cells. No systemic circulation of CHL is considered in the model.

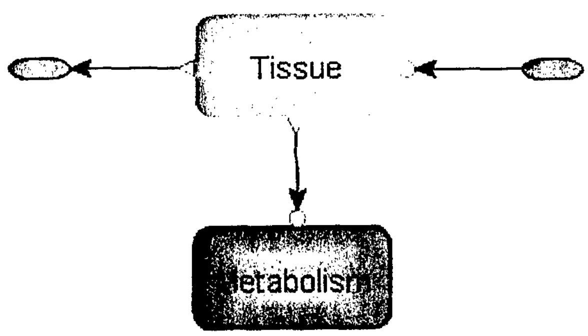
Oxidative Metabolism. Apart from the limited metabolism occurring in the lung, the model assumes that all oxidative metabolism takes place in the liver. The dose metric provided to describe metabolism is the total amount of TCE metabolized divided by the body weight. The model does not actually calculate the formation and metabolism of CHL in the liver, but instead assumes that TCA and TCOH are formed in a fixed yield from the oxidative metabolism of TCE (Figure 3b). In the model, TCOH can subsequently be oxidized to TCA or conjugated with glucuronic acid. Biliary excretion of TCOH glucuronide and enterohepatic recirculation of free TCOH are described, with only the glucuronide being excreted in the urine (Figures 3b-3e). The description of TCA includes compartments for liver, blood, and other tissues, with clearance into the urine from blood (Figure 3f). Binding of TCA in the plasma is modeled using equations derived from experimental data,[13] and only the free TCA is exchanged with the tissues. Tissue distribution is described using measured partitioning of TCA between tissues and blood.[8, 9, 16] Measured partition coefficients for total TCA between tissues and blood were converted to partitions for free TCA between tissues and plasma, assuming that all TCA in the tissue is free and using an estimate of the free fraction in plasma from the in vitro binding studies. An empirical ratio is used to adjust predicted plasma concentrations for comparison with measured blood concentrations. A rudimentary single-compartment description of DCA is included in the model, assuming direct production of DCA from TCE as a constant fraction of the rate of oxidative metabolism (Figure 3g). Dose metrics for use with the liver target tissue include the

concentrations and AUC for TCA in the plasma and liver. The concentration and AUC for TCOH in the blood are also provided as a noncancer dose metric.

Conjugative Metabolism. The model also includes a linear metabolic pathway representing conjugation of TCE by GST (Figure 3b). The model implicitly assumes that all GSH conjugation of TCE in the liver leads eventually to the appearance of DCVC in the kidney. Clearance of DCVC by N-acetyl-transferase into the urine is also modeled (Figure 3h). The dose metric provided in the model for the kidney is the total production of a thioacetylating intermediate from DCVC, divided by the volume of the kidney.

**Figure 3. Model schematics for the metabolites.** (A) Sub-model for tracheo-bronchial compartment; (B) Sub-model for liver; (C) Sub-model for TCOH and TCOG; (D) Sub-model for TCOH; (E) Sub-model for TCOG; (F) Sub-model for TCA; (G) Sub-model for DCA; (H) Sub-model for DCVC. These diagrams were taken directly from the acslXtreme graphic model display. The blocks are color coded. (Red: blood compartment. Dark Blue: venous blood compartment. Yellow: tissue compartment. Brown: metabolism compartment. Light Green: bile compartment. Dark Green: dosing compartment. Purple: excretion compartment. Light blue: submodel. Rose: mass balance compartment.)

A



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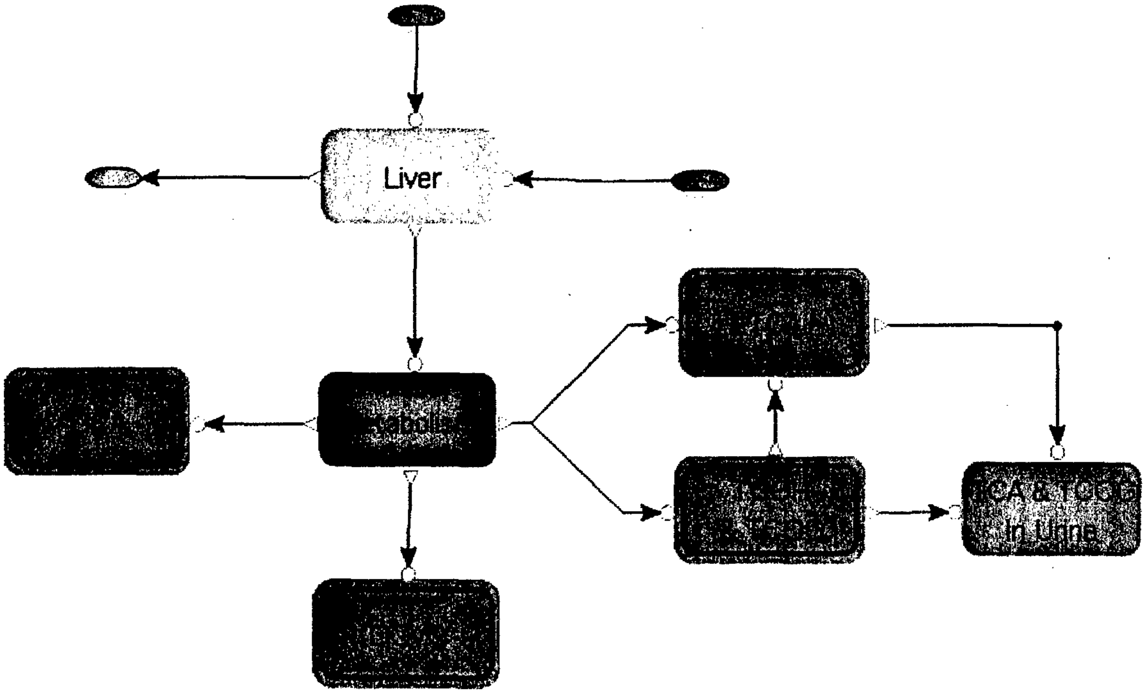


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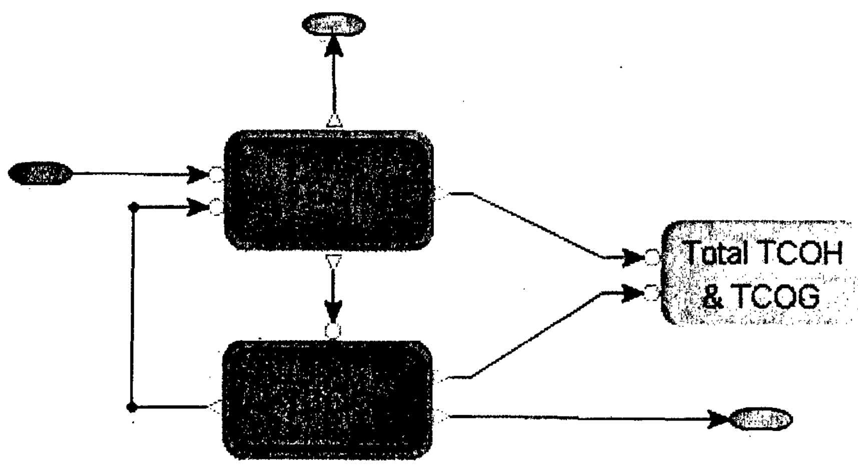

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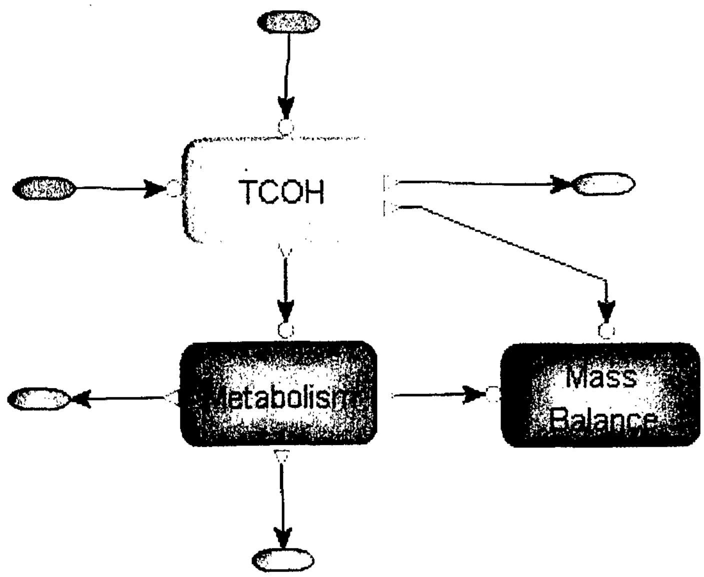
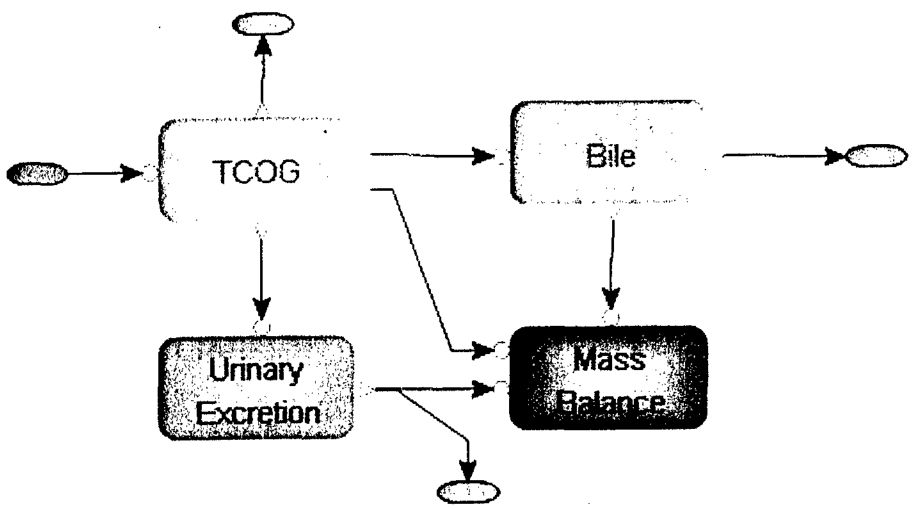


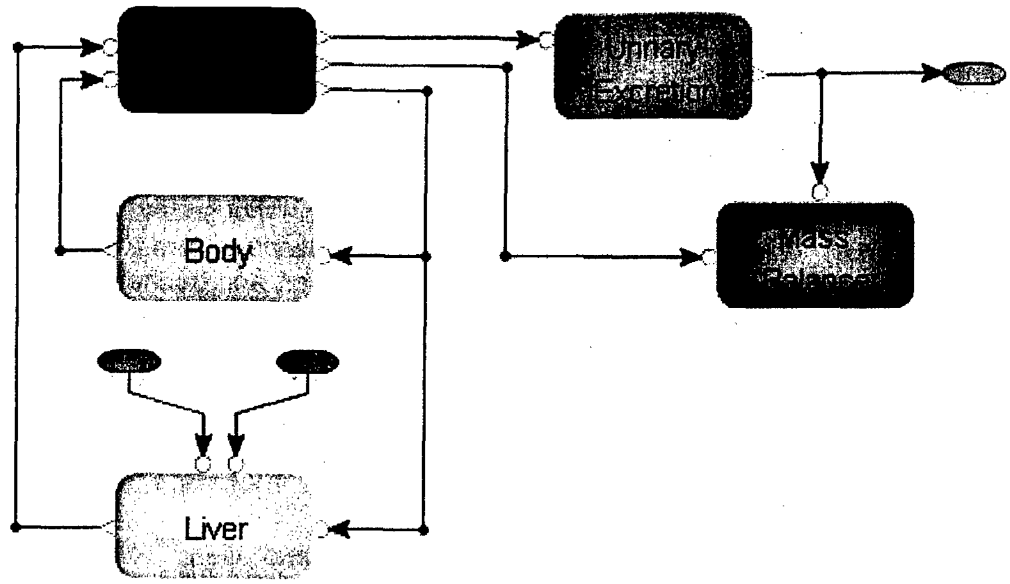
TCOH
Metabolism
Mass Balance


E

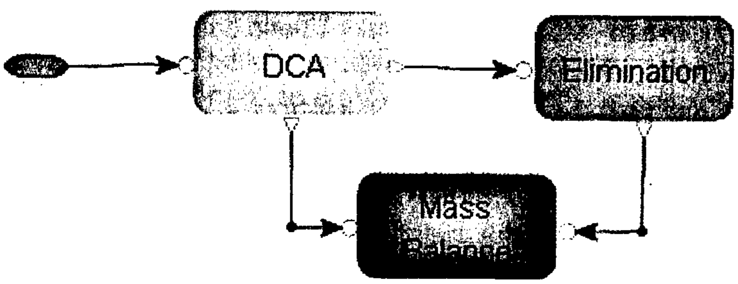


TCOG
Bile
Urinary Excretion
Mass Balance

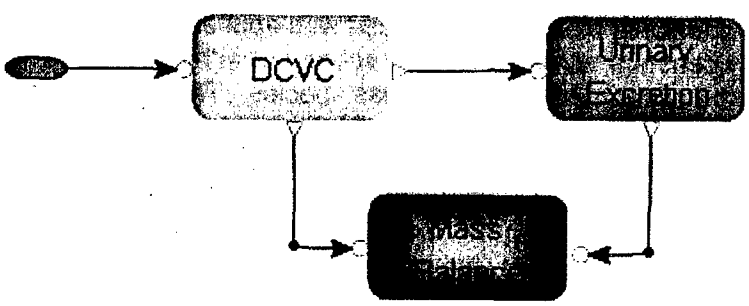
**F**


Urinary
Excretion
Mass
Balance
Body
Liver

**G**


DCA
Elimination
Mass
Balance

**H**


DCVC
Urinary
Excretion
Mass

## PBPK Model Parameters

The parameters for the model and their source references are listed in Table 1; they are discussed in the following section.

Parameters for the Parent Chemical. The physiological parameters, with two exceptions, were based on the recommendations of the ILSI Risk Science Institute Working Group on Physiological Parameters.[17] The exceptions were the cardiac output in the mouse and the alveolar ventilation in the human, which were based on the recommendations of Arms and Travis.[18] In the model, the tissue volumes and blood flows for the gut, liver, and tracheo-bronchial region are subtracted from the values shown for "all rapidly perfused tissues" to obtain the parameters for the rapidly perfused tissue compartment shown in Figure 2, and those for the fat are subtracted from the values shown for "all slowly perfused tissues" to obtain the parameters for the slowly perfused tissue compartment. The kidney volume shown in Table 1 is used only in calculations for the kidney dose-surrogate; as shown in Figure 2, the kidney is not described separately in the parent chemical model.

The partition coefficients for TCE were obtained from the work of Fisher and Allen;[5-7] the partition coefficients for the gut and tracheo-bronchial tissues were assumed to be the same as those reported for the richly perfused tissues. The oral uptake parameters were estimated from data on the appearance of TCE and its metabolites in the blood following gavage in mice and rats. For some parameters, identified in Table 1, values chosen for calculating risk assessment dose metrics were different from those chosen to reproduce pharmacokinetic data. For example, human dose metrics were calculated using a value for alveolar ventilation of 24, which corresponds to the EPA's standard assumption of a total ventilation rate of 20 $m^3$/day. Similarly, animals used in pharmacokinetic studies tend to have lower average body weights than animals used in cancer bioassays, so body weights appropriate to each case were used in the model.

Parameters for Oxidative Metabolism. Initial values for the metabolic parameters for TCE were obtained from the work of Fisher and Allen;[5-7] however, the metabolic and clearance parameters for TCA and TCOH were derived primarily on the basis of fitting the pharmacokinetic data depicted in the figures. Since the model contains a large number of metabolic and clearance parameters, many of which are highly correlated, the parameter values estimated by this process (i.e., the kinetic parameters for TCA and TCOH) cannot be considered to be unequivocally identified. However, an additional biological constraint was applied by attempting to ensure that parameters are relatively constant across exposure scenarios within a given species, and (to the extent justified by the experimental data) across species. This constraint greatly reduces the likelihood that alternative parameterizations could demonstrate equivalent success in reproducing the entire body of data. Another constraint on the parameterization not obvious from the figures is the fact that of the total TCOH extractable from the blood, roughly 80% is present as free TCOH in the human,[19] while roughly 70-85% is present as the glucuronide in the rodent.[20, 21] In the figures in this paper, the model concentrations shown represent either free TCOH or the total of TCOH plus its glucuronide, corresponding to the experimental data provided.

It is informative to note the departures from simple allometric expectations that were required on the basis of the experimental data across species. As with most other xenobiotics, the mouse shows a relatively greater, and more variable, capacity (VMC) for oxidative metabolism of TCE than the rat and human. Moreover, the Km for oxidative metabolism of TCE in the human appears to be roughly an order of magnitude larger than in the rodents. A striking difference between humans and rodents, which was clearly demanded by the experimental data, was that

the oxidation of TCOH to TCA appears to be a relatively high affinity, low capacity process in the rodent but low affinity, high capacity in the human. It may be that this disparity reflects the involvement of different enzymes (e.g., MFO in the rodent *vs.* ADH in the human). The result of this species difference is that although the model uses a similar value across species for PO (based on the initial split of TCA and TCOH from CHL), the apparent ratio of TCA to TCOH predicted (and observed) over the entire time-frame of an exposure to TCE is much higher in the human than in the rodent. The apparent capacity for glucuronidation of TCOH in the human, on the other hand, is much lower than in the rodent, as reflected in the greatly different ratios of free TCOH to glucuronide in the blood, mentioned above.

Parameters for Lung Metabolism. The parameters in the PBPK model for predicting the lung dose metric are the capacity and affinity for the production of CHL, and the capacity and affinity for its clearance. In the model, the production of CHL in the tracheobronchial region was assumed to be associated with the P450 activity in that tissue. This is the assumption that was made in the pharmacokinetic risk assessment for methylene chloride.[15] The approach used in that risk assessment was also used to obtain the parameters in this case: the affinity in the lung was assumed to be the same as in the liver for the same species, and the relative capacity of the lung compared to the liver was determined on the basis of P450 activity measured with standard substrates.[15] Based on these data, P450 activity falls off much more rapidly with body weight than would be expected from allometric considerations. No data was available on the clearance of CHL in the lung across species, therefore it was assumed to be a low affinity, high capacity enzyme system such as ADH. The parameters in the PBPK model were chosen such that concentrations of CHL in the lung of the mouse predicted by the model were consistent with those observed in experimental studies.[8] It was further assumed that the clearance of CHL in the lung scales across species according to allometric expectations (i.e., by body weight to the 3/4 power). This assumption leads to much lower CHL concentrations in the lungs of rats and humans compared to mice for the same TCE exposure conditions. An alternative assumption was that the activity of the enzyme responsible for the clearance of CHL scales in the same way as P450; this assumption leads to similar concentrations of CHL in the lungs of mice, rats and humans for the same TCE exposure conditions.

Parameters for Conjugative Metabolism. The parameters in the PBPK model for predicting the kidney dose metric are the production of DCVC by the GST pathway, its activation by beta-lyase, and its clearance by N-acetyl-transferase. First-order rate constants are used because the production of metabolites by the GST pathway is quite low, and saturation of enzyme capacity is unlikely. The capacity and affinity of beta-lyase in the kidney have been measured in both rats and humans.[22] This data was used to estimate the apparent first-order rate constants used in the model. No data was available on the activity of beta-lyase in the mouse, so the relationships between beta-lyase metabolic parameters in mice and rats reported for trichlorovinylcysteine derived from perchloroethyene[23] were assumed to apply for DCVC as well. For N-acetyl-transferase, only specific activity data across species is available.[24] These data were converted to the corresponding rate constants by assuming the affinity of N-acetyl-transferase for DCVC is the same as that measured for beta-lyase in the same species. This assumption is supported by the similarity of the affinities of N-acetyl-transferase and beta-lyase for DCVC in the rat: 3.3 mM and 1.6 mM, respectively.[22, 25]

Finally, measurements of oxidative and conjugative metabolites in the urine following TCE exposure[26] were used to obtain estimates of the GST pathway rate constant. The oxidative pathway was represented by total excretion of TCA plus TCOH, while the conjugative pathway was represented by excretion of 1,2-DCVC. Data from the same study on excretion of 2,2-DCVC was not used. Unlike 1,2-DCVC, there was no evidence of a dose-response for 2,2-

DCVC as a function of TCE exposure in humans or rodents; similar amounts of 2,2-DCVC were excreted for TCE exposures ranging from 40 to 160 ppm. The results of this analysis[1] indicated that the model could be made to agree quite well with the urinary data when allometric scaling was assumed for conjugative metabolism.

## Table 1: Model Parameters

| | | Mouse | | Rat | | Human | |
|---|---|---|---|---|---|---|---|
| | Parameter | Value | Reference | Value | Reference | Value | Reference |
| BW | Body Wt (kg) | 0.035[1] | EPA default | 0.35[1] | EPA default | 70.0[1] | ICRP (International Commission on Radiological Protection (ICRP) 1975) |
| QCC | Cardiac output | 18.0 | USEPA (U.S. Environmental Protection Agency (USEPA) 1988) | 15.0 | Brown *et al.* (Brown, Delp *et al.* 1997) | 13.0 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QPC | Pulmonary ventilation | 30.0[2] | Brown *et al.* (Brown, Delp *et al.* 1997) | 24.0[3] | Brown *et al.* (Brown, Delp *et al.* 1997) | 18.0 | Astrand and Rodahl (Astrand and Rodahl 1970) |
| QFatC | Fat | 0.07 | Rat value | 0.07 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.052 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QGutC | Gut | 0.141 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.162 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.181 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QLivC | Liver | 0.02 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.021 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.046 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QRapC | Rapidly perfused tissues | 0.713 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.594 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.699 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QSlwC | Slowly perfused tissues | 0.287 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.406 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.301 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| QTBC | Tracheo-bronchial | 0.005 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.021 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.025 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VBldC | Blood | 0.049 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.074 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.079 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VBodC | Total body | 0.2 | Fit to data from Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.2 | Fit to data from Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.2[3] | Fit to data from Muller *et al.* (Muller, Spassovski *et al.* 1974), (Muller, Spassovski *et al.* 1975) |
| VFatBldC | Fraction of fat that is blood | 0.02 | Human value | 0.02 | Human value | 0.02 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VFatC | Fat | 0.07[3] | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.07 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.214 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VGutC | Gut | 0.042 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.027 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.017 | Brown *et al.* (Brown, Delp *et al.* 1997) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| VKidC | Kidney | 0.017 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.007 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.004 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VLivC | Liver | 0.055 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.034 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.026 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VRapC | Rapidly perfused tissues | 0.217 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.213 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.192 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VSlwC | Slowly perfused tissues | 0.619 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.664 | Brown *et al.* (Brown, Delp *et al.* 1997) | 0.651 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VTBC | Tracheo-bronchial | 0.0007 | Brown *et al.* (Brown, Delp *et al.* 1997); Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0005 | Brown *et al.* (Brown, Delp *et al.* 1997); Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0008 | Brown *et al.* (Brown, Delp *et al.* 1997) |
| VDDCAC | DCA | 0.5 | Schultz *et al.* (Schultz, Merdink *et al.* 2002) | 0.5 | Saghir and Schultz (Saghir and Schultz 2003) | 0.26 | Curry *et al.* (Curry, Chu *et al.* 1985) |
| VDTCOHC | TCOH | 0.65 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.65 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.65 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| PB | Blood/air | 14.0 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 18.5 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 9.2 | Allen and Fisher (Allen and Fisher 1993) |
| PFat | Fat/blood | 36.0 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 27.5 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 73.0 | Allen and Fisher (Allen and Fisher 1993) |
| PGut | Gut/blood | 1.8 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 1.3 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 6.8 | Allen and Fisher (Allen and Fisher 1993) |
| PLiv | Liver/blood | 1.8 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 1.3 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 6.8 | Allen and Fisher (Allen and Fisher 1993) |
| PRap | Rapidly perfused/blood | 1.8 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 1.3 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 6.8 | Allen and Fisher (Allen and Fisher 1993) |
| PSlw | Slowly perfused/blood | 0.75 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.5 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 2.3 | Allen and Fisher (Allen and Fisher 1993) |
| PTB | TB/blood | 1.8 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 1.3 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 6.8 | Allen and Fisher (Allen and Fisher 1993) |
| PAFatC1 | Takeup | 10.0 | Set to over ride two-compartment fat | 10.0 | Set to over ride two-compartment fat | 10.0 | Set to over ride two-compartment fat |
| PAFatC2 | Release | 10.0 | Set to over ride two-compartment fat | 10.0 | Set to over ride two-compartment fat | 10.0 | Set to over ride two-compartment fat |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PBodTCA | Body/free plasma | 0.76 | Abbas and Fisher (Abbas and Fisher 1997); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 0.51 | Jepson *et al.* (Jepson, Hoover *et al.* 1994); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 1.9 | Fisher *et al.* (Fisher, Mahle *et al.* 1998); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) |
| PLivTCA | Liver/free plasma | 1.14 | Abbas and Fisher (Abbas and Fisher 1997); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 0.76 | Jepson *et al.* (Jepson, Hoover *et al.* 1994); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 2.5 | Fisher *et al.* (Fisher, Mahle *et al.* 1998); Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) |
| VMaxC | Oxidative capacity (mg/hr) | 32.7 [3] | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 11.2 [3] | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 12.0 [3] | Allen and Fisher (Allen and Fisher 1993) |
| KM | Oxidative affinity (mg/L) | 0.25 | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.25 [3] | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 1.5 | Allen and Fisher (Allen and Fisher 1993) |
| kDCVCC | Production of DCVC(/hr) | 0.015 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.015 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.015 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| FracDCA | Fractional split of TCE to DCA | 0.04 | Fit to data from Templin *et al.* (Templin, Parker *et al.* 1993) | 0.04 | Mouse value | 0.004 | Fit to data from Fisher *et al.* (Fisher, Mahle *et al.* 1998) |
| FracTCE | Fractional split of TCE to TCA | 0.035 | Fit to data from Prout *et al.* (Prout, Provan *et al.* 1985) | 0.04 [3] | Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.08 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| VMaxClaraC | VMax | 3.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.3 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0045 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| KMClara | KM | 0.25 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.25 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 1.5 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| VMaxClearC | VMax for chloral clearance | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| KMClear | KM for chloral clearance | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 250.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kDissoc | Protein/TCA dissociation constant (µmole/L) | 46.1 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 383.6 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 174.6 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) |
| NumSites | Number of binding sites per class protein | 0.17 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 1.49 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 2.97 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) |
| ProtConc | Protein concentration (µmoles/L) | 196.0 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 190.0 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) | 239.0 | Lumpkin *et al.* (Lumpkin, Dallas *et al.* 2003) |
| VMaxTCOHC | VMax for oxidation to TCA | 1.0 [3, 4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.12 [3, 4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 25.0 [3,4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| KMTCOH | KM for oxidation to TCA | 0.25 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.25 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 250.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| VMaxGlucC | VMax for glucuronidation to TCOG | 100.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 100.0 [3,4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 5.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| KMGluc | KM for glucuronidation to TCOG | 25.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 25.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 25.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kNATC | Clearance of DCVC by NAT | 0.5 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 1.1 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 19.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kKidCytoC | Kidney cytotoxicity from DCVC | 0.4 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 17.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 37.0 | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kAS | Stomach to gut | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kTSD | Stomach to duodenum | 10.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 10.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 10.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kAD | Duodenum to liver | 0.6 [3] | Fit to data from Prout *et al.* (Prout, Provan *et al.* 1985) | 0.3 [3] | Fit to data from Templin *et al.* (Templin, Stevens *et al.* 1995) | 1.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kTD | Fecal excretion | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kBileC | Biliary excretion of TCOG | 1.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 1.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 1.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kEHRC | Enterohepatic recirculation of TCOH | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [3,4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| kClearDCAC | Clearance of DCA | 1.0 | Schultz *et al.* (Schultz, Merdink *et al.* 2002) | 1.3 | Saghir and Schultz (Saghir and Schultz 2003) | 1.9 | Curry *et al.* (Curry, Chu *et al.* 1985) |
| kUrnTCAC | Urinary excretion of TCA | 0.3 [3] | Fit to data from Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.3 | Fit to data from Fisher *et al.* (Fisher, Gargas *et al.* 1991) | 0.2 [3] | Fit to data from Muller *et al.* (Muller, Spassovski *et al.* 1974), (Muller, Spassovski *et al.* 1975) |
| kUrnTCOGC | Urinary excretion of TCOG | 0.5 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 0.5 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) | 3.0 [4] | Clewell *et al.* (Clewell, Gentry *et al.* 2000) |
| FracPlas | Fraction of blood that is plasma | 0.58 | Human value | 0.58 | Human value | 0.58 | ICRP (International Commision on Radiological Protection (ICRP) 1975) |
| TCAPlas | To convert TCA in plasma to TCA in blood | 0.76 | Personal communication with Jeff Fisher | 0.76 | Personal communication with Jeff Fisher | 0.76 | Personal communication with Jeff Fisher |

[1] Used study specific values when available.
[2] 18.0 was used for open chamber simulations. 30.0 was used for closed chamber simulations.
[3] Different values were needed to fit some data sets.
[4] Value from Clewell *et al.* (Clewell, Gentry *et al.* 2000) was fit to data.

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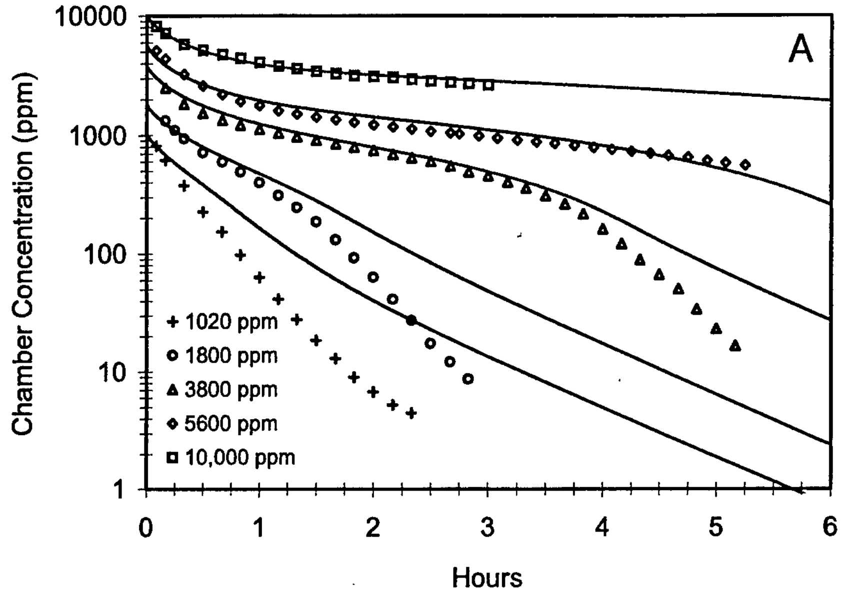
## RESULTS

The predictions of the PBPK model for the experimental data sets used in its development are shown in Figures 4-17. The order of the figures follows the order of use of the data in model development. Mouse data sets are shown first, followed by rat and human.

Figure 4 shows the ability of the model to simulate the chamber concentration time-course in gas-uptake studies conducted with male (a) and female (b) B6C3F1 mice. These data were used to obtain initial estimates of the kinetic parameters for TCE.[5] The resulting estimates of VmaxC were 32.7mg/hr/kg$^{3/4}$ for the male and 23.2 mg/hr/kg$^{3/4}$ for the female. Fractional fat volumes of 0.05 and 0.1 were also estimated for males and females, respectively, based on the early uptake in these studies. It was only possible to determine that Km was probably less than 1ug/L. Estimates of the other kinetic parameters were obtained using data on concentrations of TCE and its metabolites in male mice following oral gavage in corn oil[27] and water[20] vehicles.

The resulting fits of the model to the data are shown in Figures 5 and 6. In fitting these two data sets, it was only necessary to use different values for three of the model kinetic parameters. The simulation of the corn oil gavage data was obtained with kAD=0.3, VmaxC=50, and VmaxTCOHC=2, while the aqueous vehicle data was best simulated with kAD=1.0, VmaxC=60, and VmaxTCOHC=0.5. For both data sets, it was also necessary to reduce QPC to 18 L/hr/kg$^{3/4}$, rather than the value of 30 L/hr/kg$^{3/4}$ used in the closed chamber studies. The rest of the model parameters were as shown in Table 1.

**Figure 4. Comparison of predicted and experimental chamber concentrations of TCE in male (A) and female (B) B6C3F1 mice exposed to TCE in a closed, recirculating chamber.** Kinetic data are taken from Fisher *et al.*[5]



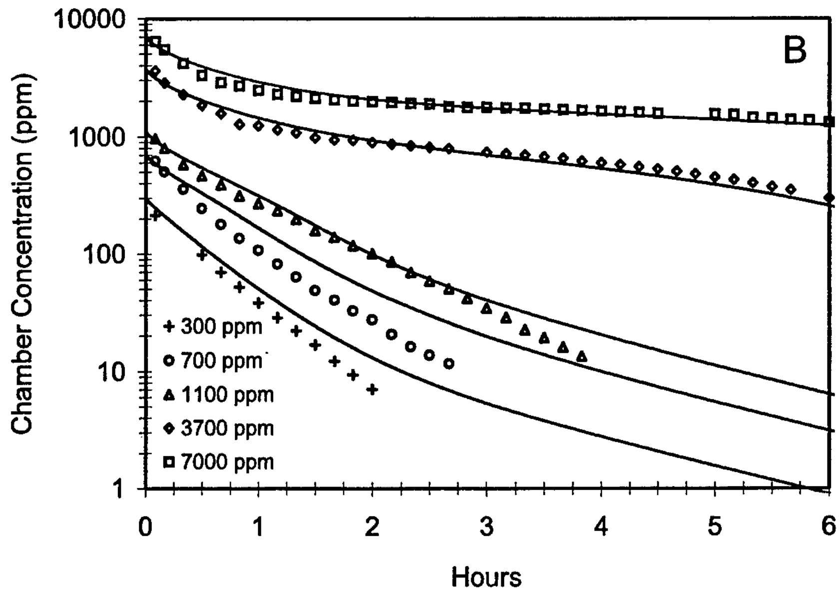



**Figure 5. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following corn oil gavage with 1000 mg/kg TCE in mice.** Kinetic data are taken from Prout *et al.*[27]

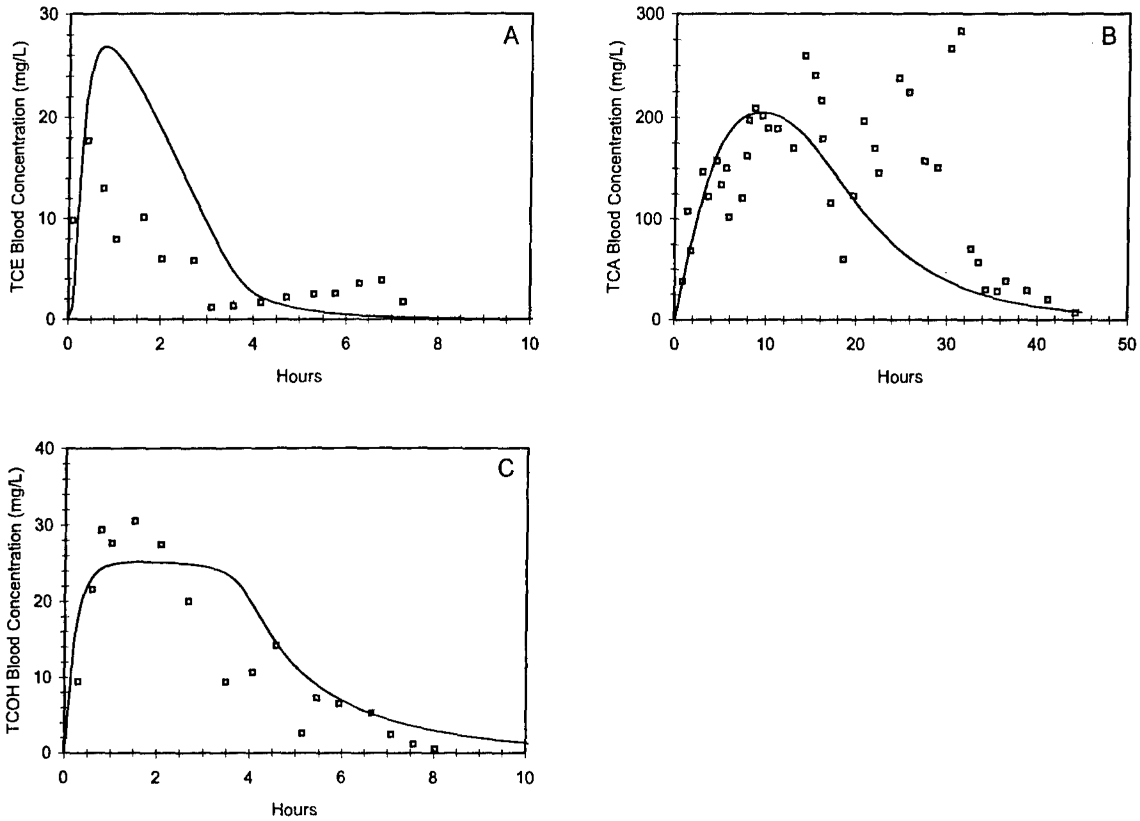


**Figure 6. Mean observed and predicted blood concentrations of (A) TCE and metabolites (B) TCA, (C) TCOH and (D) DCA following an oral dose of 499 mg/kg TCE in B6C3F1 mice.** Kinetic data are taken from Templin *et al.*[20]

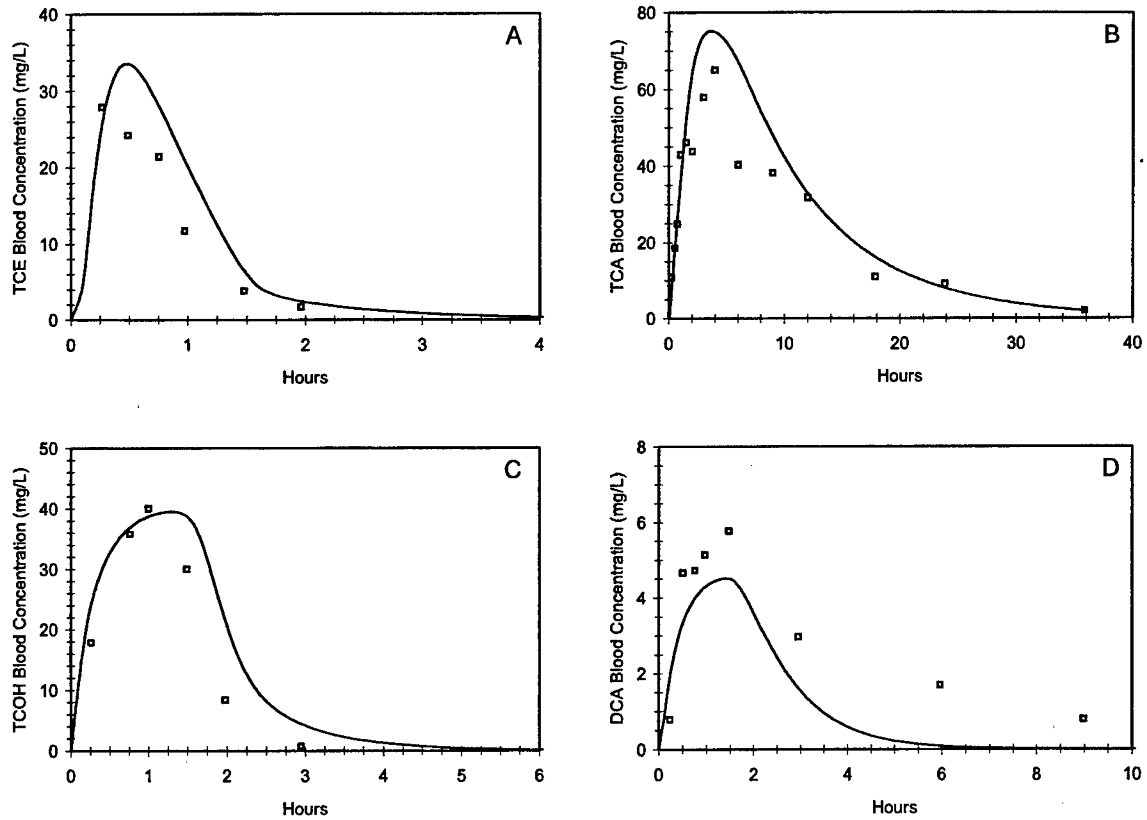



Figure 7 shows the predictions of the model for inhalation exposures to TCE in male and female mice.[5] All of the model parameters in this case were those shown in Table 1, except that for the females the value of VmaxC was reduced to 23.2 mg/hr/kg$^{3/4}$ and the urinary excretion rate constant for TCA, kUrnTCAC, was doubled to 0.6 kg$^{1/4}$/hr. The lower value of QPC mentioned above was also used. Validation of these mouse parameter values, shown in Figure 8 was performed using the more recent inhalation data of Greenberg *et al.*[11].

Finally, the model parameters in Table 1 were tested by using them in the model to predict the time-course for TCE and TCA in a number of tissues for comparison with the corn oil gavage data collected by Abbas *et al.*[8]; the results of the prediction are displayed in Figure 9. The blind predictions of the model are generally within a factor of two of the data, although the model tends to underestimate TCE concentrations at early times. The model also overestimates liver concentrations of TCA to a much greater extent than blood concentrations, suggesting that the *in vitro* partitioning of TCA may not accurately predict its distribution *in vivo*.

**Figure 7. Comparison of predicted and experimental concentrations of TCE in blood and TCA in plasma in B6C3F1 mice exposed to TCE by inhalation.** The figures show TCE-blood and TCA-plasma concentrations in (A) male mice exposed for 4 hr to 110 ppm TCE vapors and (B) female mice exposed for 4 hr to 368 ppm TCE vapors. Kinetic data are taken from Fisher *et al.*[5]

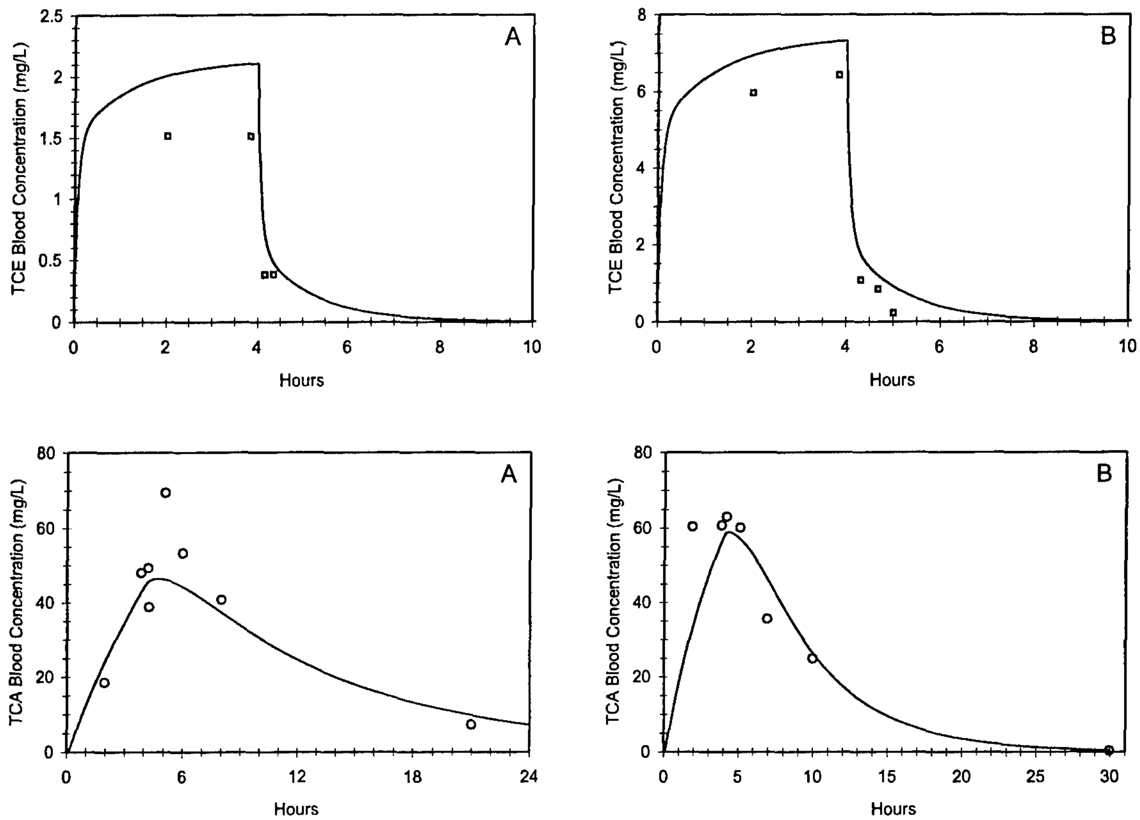


**Figure 8. Comparison of predicted and experimental concentrations of TCE, TCOH, and TCA in blood in male B6C3F1 mice exposed for 4 hr to 600 ppm TCE by inhalation.** Kinetic data are taken from Greenberg *et al.*[11]

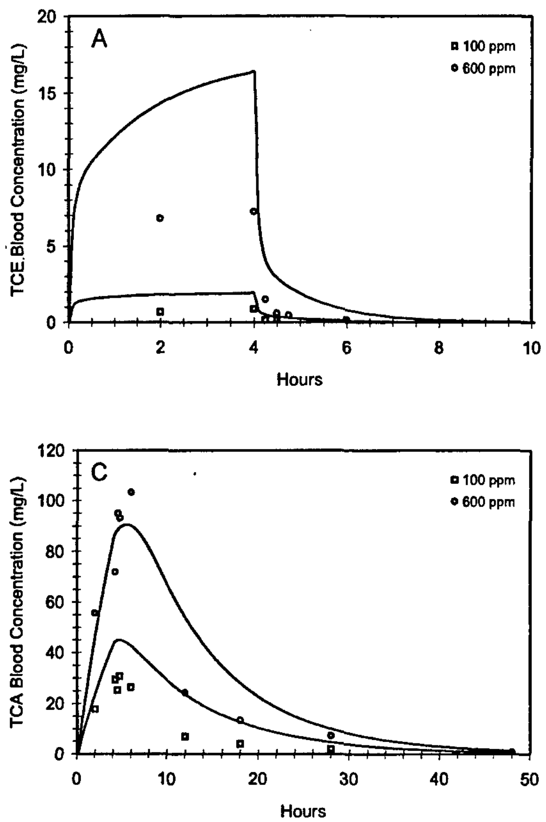
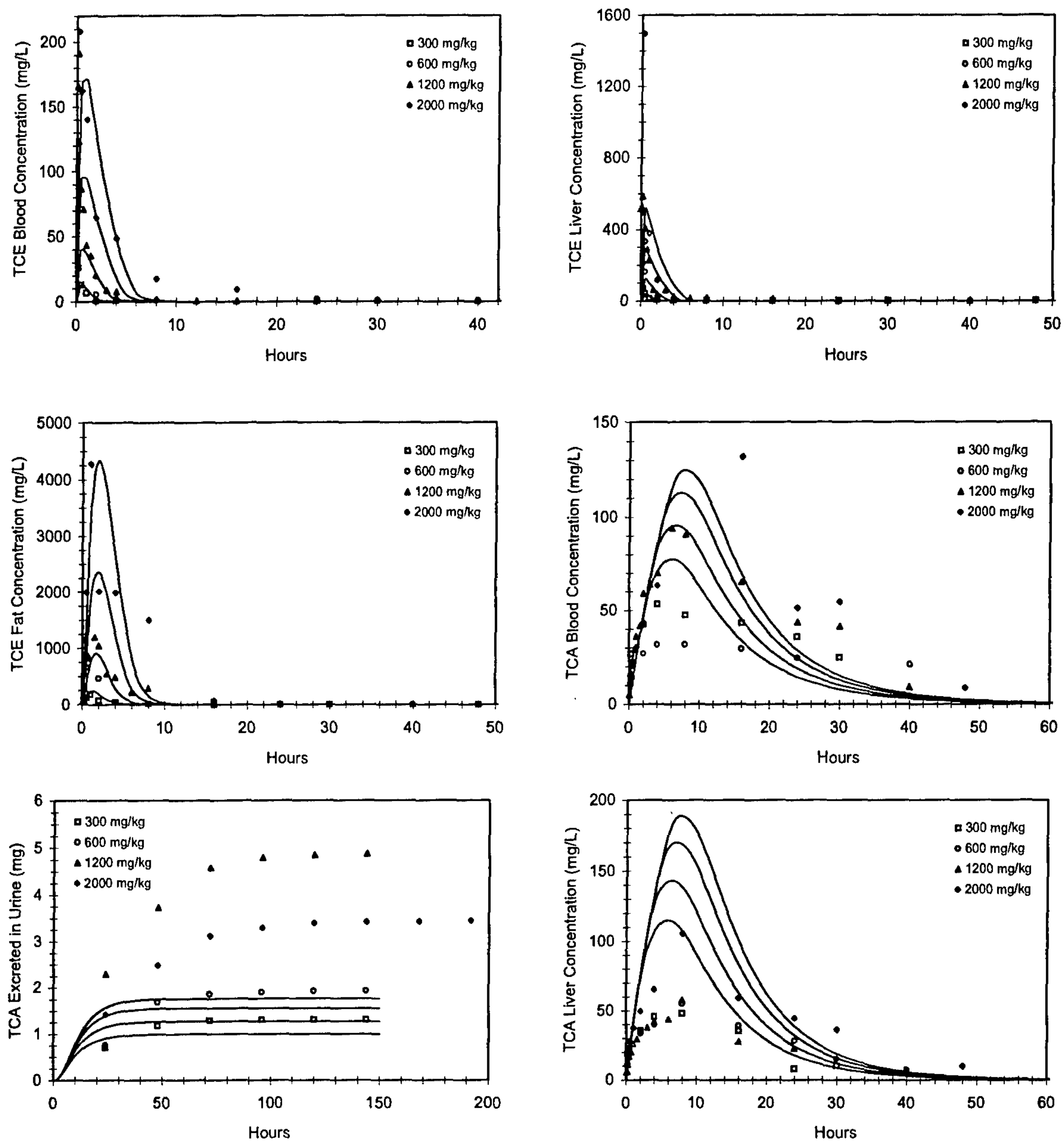


**Figure 9. Comparison of predicted and experimental concentrations of TCE in blood, liver, and fat, and TCA in blood, liver, and urine in B6C3F1 mice exposed to 300, 600, 1200, and 2000 mg/kg TCE by gavage in corn oil.** Kinetic data are taken from Abbas *et al.*[8]




The parameterization of the model in the rat followed a similar approach to that just presented for the mouse. Figure 10 shows the simulation of the gas uptake data for male rats;[28] the resulting estimate of VmaxC was 11.2 mg/hr/kg$^{3/4}$. Estimates of the other kinetic parameters were obtained using data on concentrations of TCE and its metabolites in male rats following oral gavage in corn oil[27] and water[29] vehicles. The resulting fits of the model to these data sets are shown in Figures 11 and 12. In fitting these two data sets, it was only necessary to use different values for two of the model kinetic parameters. The simulation of the corn oil gavage

data was obtained with FracTCE=0.04 and VMaxGlucC=100, while the aqueous vehicle data was best simulated with FracTCE=0.02 and VmaxGlucC=20. The rest of the model parameters were as shown in Table 1 for both simulations.

Figure 13 shows the predictions of the model for inhalation exposures to TCE in male and female rats.[5] All of the model parameters in this case were those shown in Table 1 except that for the females the value of VmaxC was increased to 20 $mg/hr/kg^{3/4}$ and the alveolar ventilation rate was decreased to 15 $L/hr/kg^{3/4}$.

**Figure 10. Comparison of predicted and experimental chamber concentrations of TCE in male F344 rats exposed to TCE in a closed, recirculating chamber.** Kinetic data are taken from Andersen *et al.*[28]

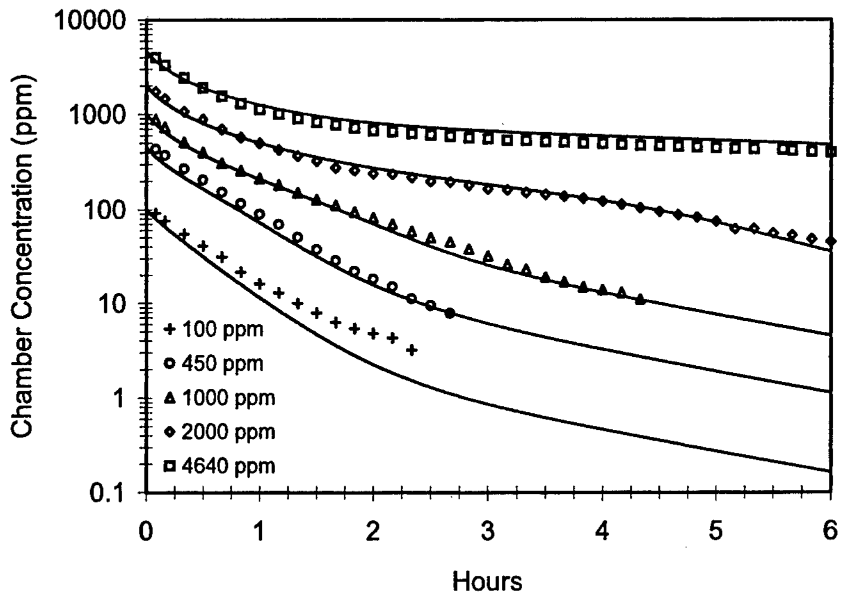


**Figure 11. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following corn oil gavage with 1000 mg/kg TCE in rats.** Kinetic data are taken from Prout *et al.*[27]

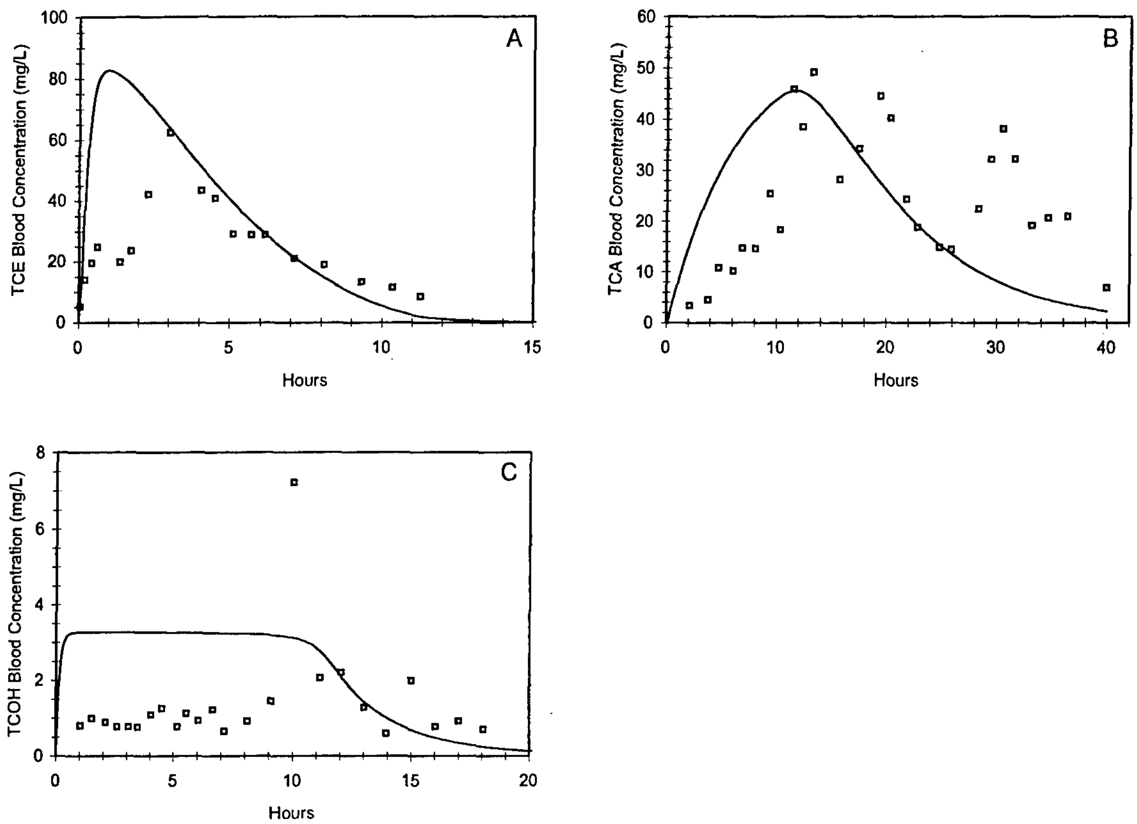


**Figure 12. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following oral doses of 200, 600, and 3000 mg/kg TCE in F-344 rats.** Kinetic data are taken from Larson and Bull.[29]

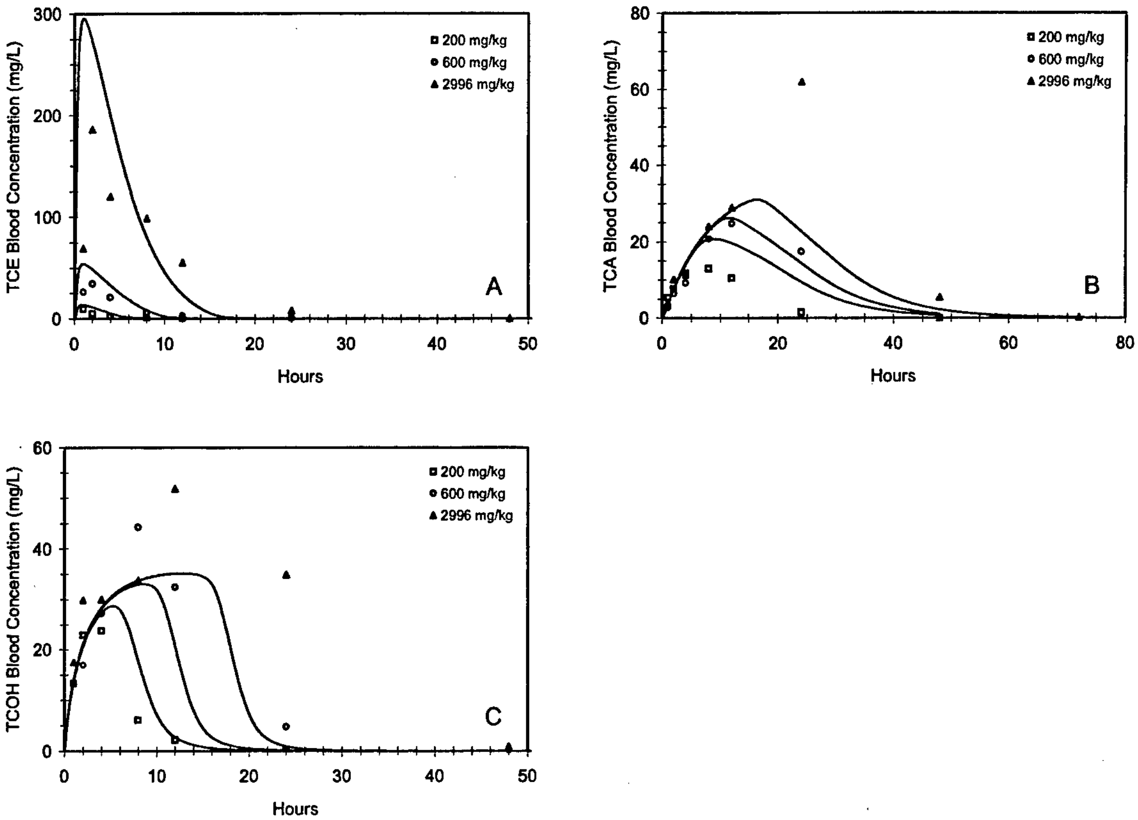
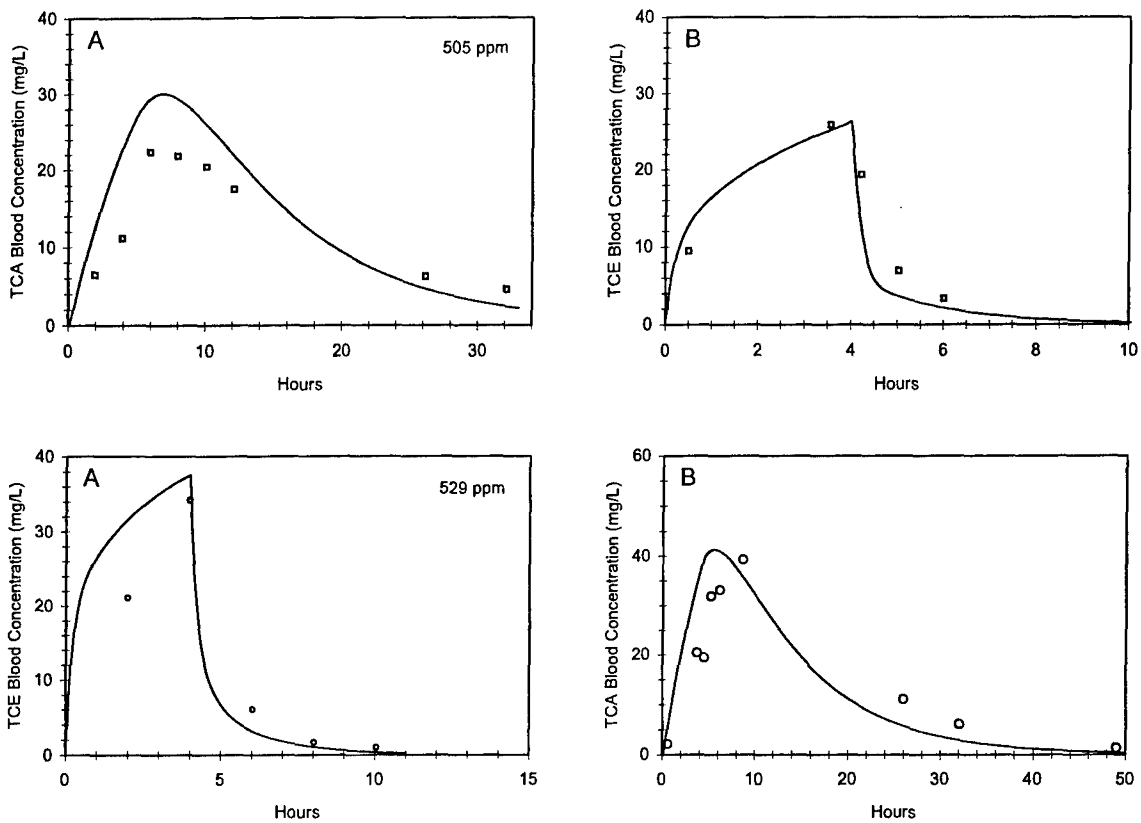


**Figure 13. Comparison of predicted and experimental concentrations of TCE in blood and TCA in plasma in F-344 rats exposed to TCE by inhalation.** The figures show (A) TCE blood concentrations in male rats exposed for 4 hr to 529 ppm TCE vapors and TCA plasma concentrations in male rats exposed for 4 hr to 505 ppm TCE vapors and (B) TCE blood and TCA plasma concentrations in female rats exposed for 4 hr to 600 ppm TCE vapors. Kinetic data are taken from Fisher *et al.*[5]




Parameterizing the human model is complicated by the fact that inter-individual variation tends to be greater in humans than in in-bred experimental animals. In particular, three of the parameters in the model were found to vary significantly across studies: VmaxC, the capacity of the oxidative metabolism of TCE, VmaxTCOHC, the capacity of the oxidative metabolism of TCOH, and kUrnTCAC, the rate constant for excretion of TCA. The greatest variation was found for VmaxC; values needed to simulate different experimental subjects ranged from 1.5 to 18 mg/hr/kg$^{3/4}$. This 10-fold variation is consistent with other observations of the variability in CYP2E1 metabolism in humans. The variation in the value of kUrnTCAC was similar, ranging from 0.05 to 0.6 kg$^{1/4}$/hr, while that for VmaxTCOHC was not as great, with values ranging from 12 to 40 mg/hr/kg$^{3/4}$. The results of fitting several published human studies[9, 19, 30-32] are shown in Figures 14 – 19. The caption to each figure shows the values of the three parameters discussed above that were used to obtain the simulation displayed.

**Figure 14. Mean observed and predicted kinetics of TCE and its metabolites during and after a single 6-hr exposure of human subjects to 100 ppm TCE.** The simulation was obtained with VmaxC=12, VmaxTCOHC=25, kUrnTCAC=0.15, and VBodC=0.12. Kinetic data are taken from Muller *et al.*:[19, 30] (A) TCE blood concentrations (mg/L); (B) TCA plasma concentrations (mg/L); (C) cumulative urinary TCA excretion (mg); (D) total TCOH plasma concentrations (mg/L); (E) cumulative urinary TCOH excretion (mg).

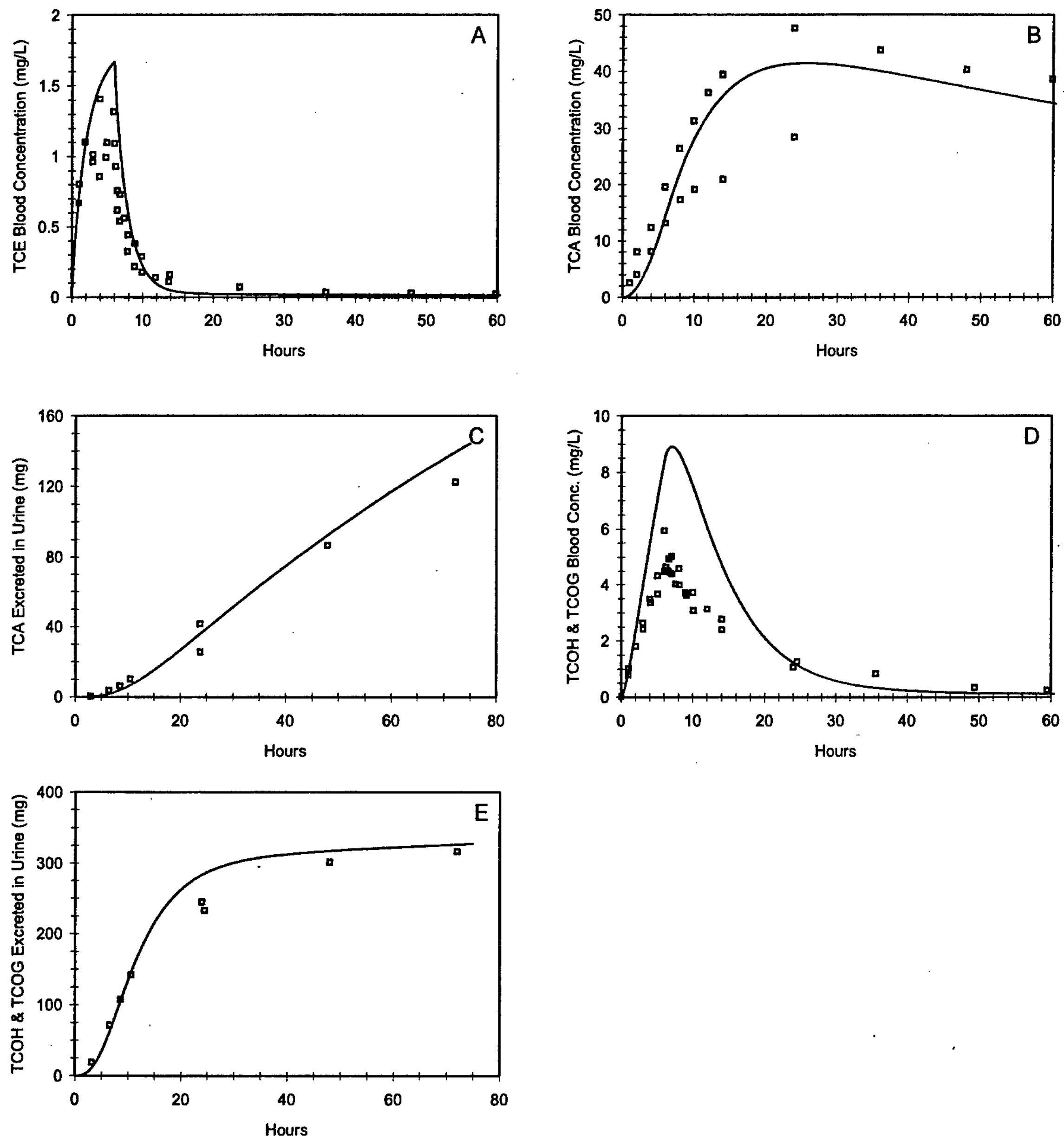


**Figure 15. Mean observed and predicted kinetics of TCE and its metabolites during and after 4-hr exposures of human subjects to 70 ppm TCE for 5 days.** The simulation was obtained with VmaxC=18, VmaxTCOHC=12, kUrnTCAC=0.15, and VBodC=0.12. Kinetic data are taken from Monster *et al.*:[31] (A) TCE venous blood concentrations (mg/L); (B) TCA plasma concentrations (mg/L); (C) cumulative urinary TCA excretion (mg); (D) cumulative urinary TCOH excretion (mg).

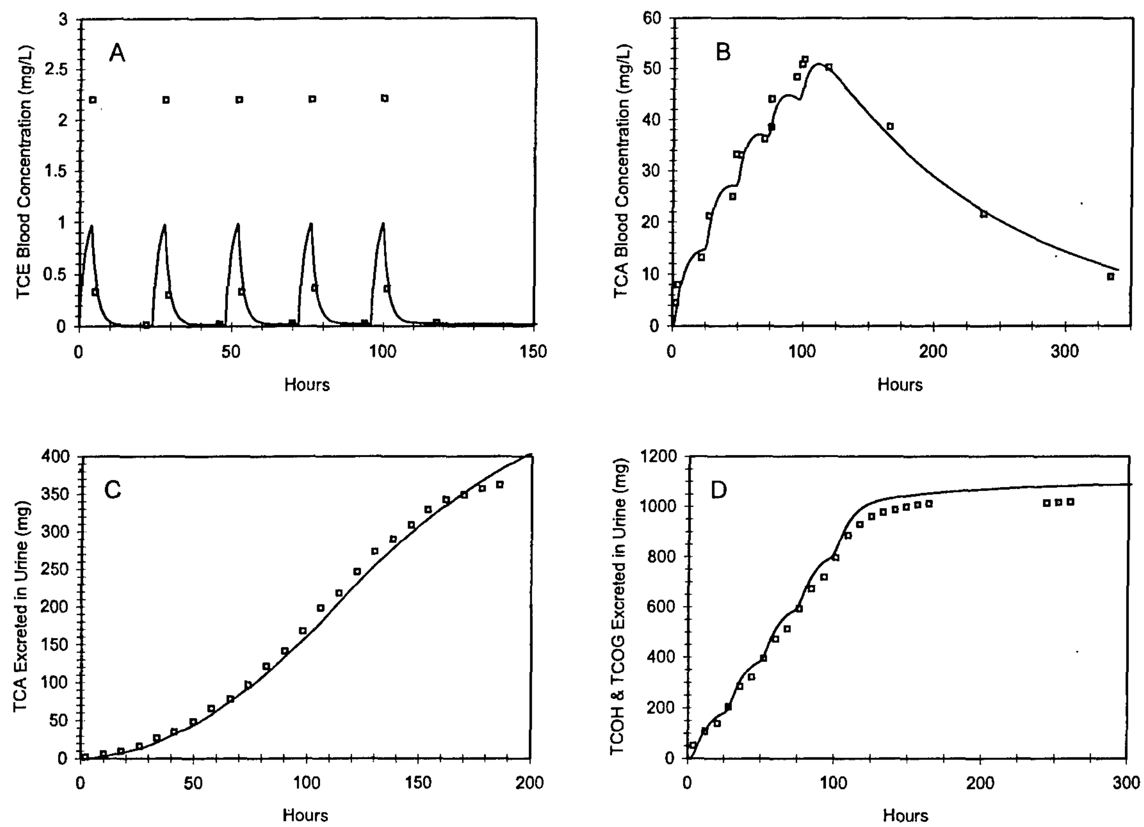


**Figure 16. Mean observed and predicted kinetics of TCE and its metabolites during and following interrupted, 7-hr exposures of human subjects to 200 ppm TCE (3 hr of exposure, a one-half hour break, then 4 hr of exposure) for 5 days.** The simulation was obtained with VmaxC=5, VmaxTCOHC=25, kUrnTCAC=0.2, and VBodC=0.2. Kinetic data are taken from Stewart *et al.*:[32] (A) TCE concentration in exhaled breath (ppm); (B) cumulative urinary TCA excretion (mg); (C) cumulative urinary TCOH excretion (mg).

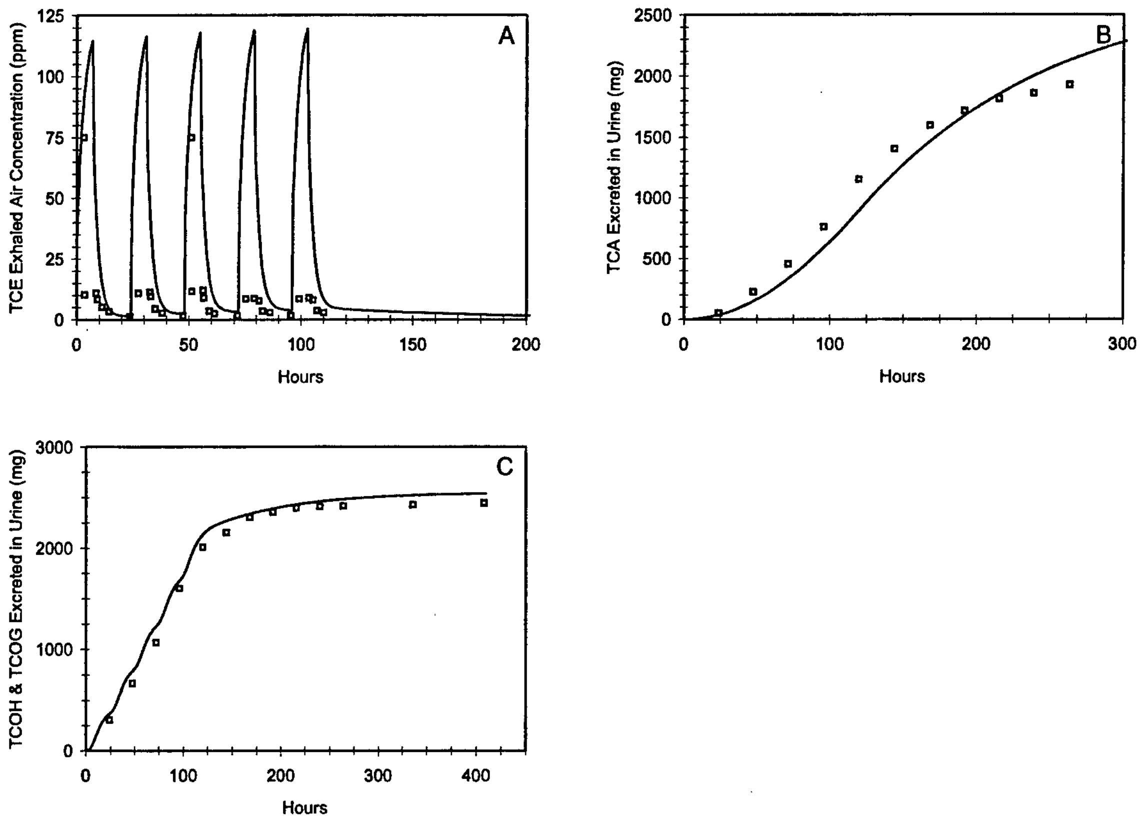


**Figure 17. Mean observed and predicted kinetics of TCE and its metabolites during and after 6-hr exposures of human subjects to 50 ppm TCE for 5 days.** The simulation was obtained with VmaxC=8, VmaxTCOHC=30, kUrnTCAC=0.2, and VBodC=0.2. Kinetic data are taken from Muller *et al.*[30] (A) TCA plasma concentrations (mg/L); (B) cumulative urinary TCA excretion (mg); (C) total TCOH plasma concentrations (mg/L); (D) cumulative urinary TCOH excretion (mg).

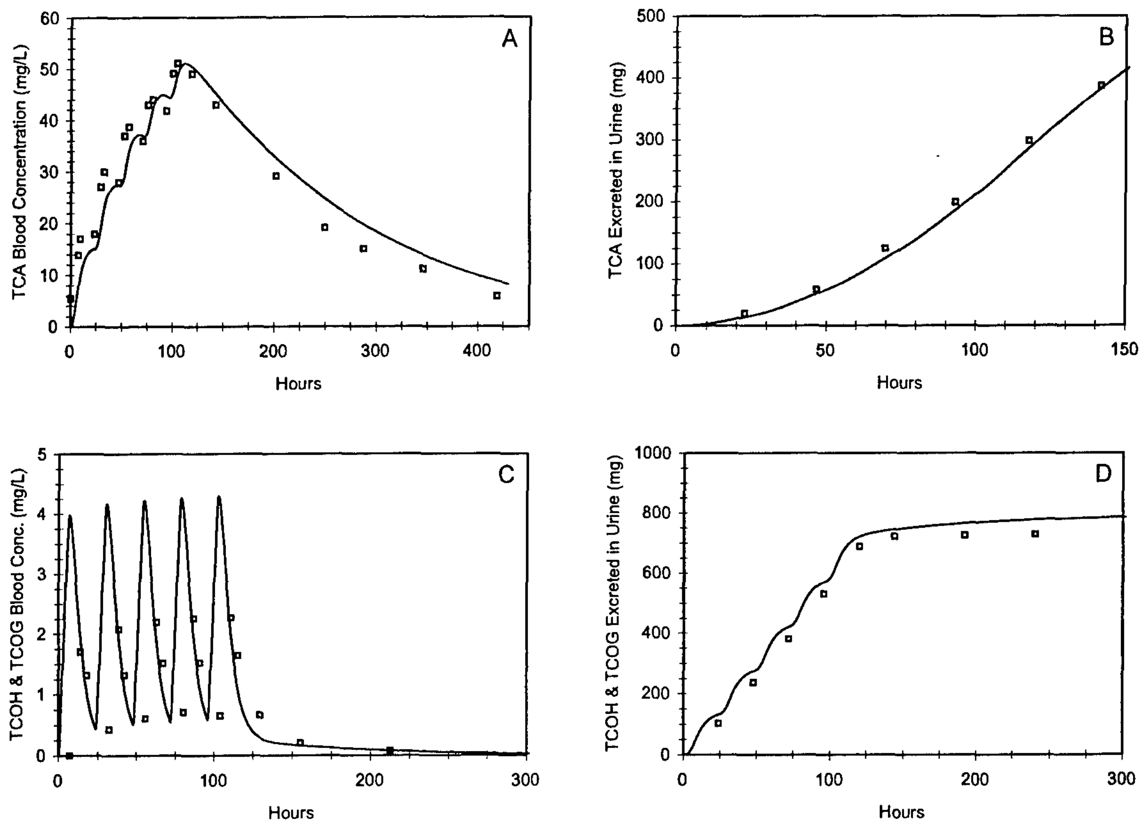


**Figure 18. Observed and predicted kinetics of TCE and its metabolites TCA, TCOH, and DCA, as well as urinary excretion of TCA and TCOH, during and after a 4-hr exposure of a male human subject to 100 ppm TCE.** The simulation was obtained with VmaxC=3, VmaxTCOHC=25, kUrnTCAC=0.2, and VBodC=0.2. Kinetic data are taken from Fisher *et al.*:[9]

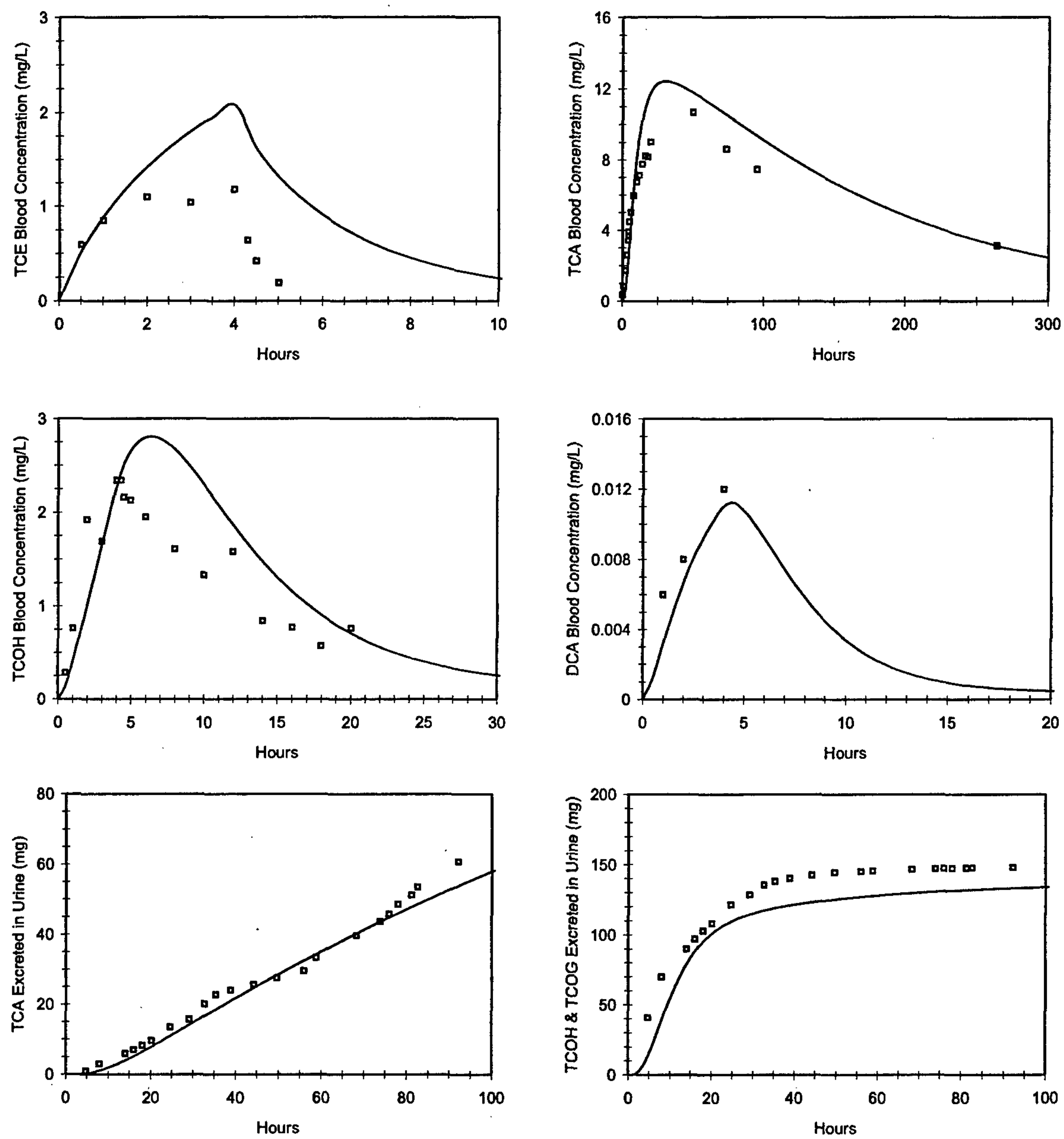
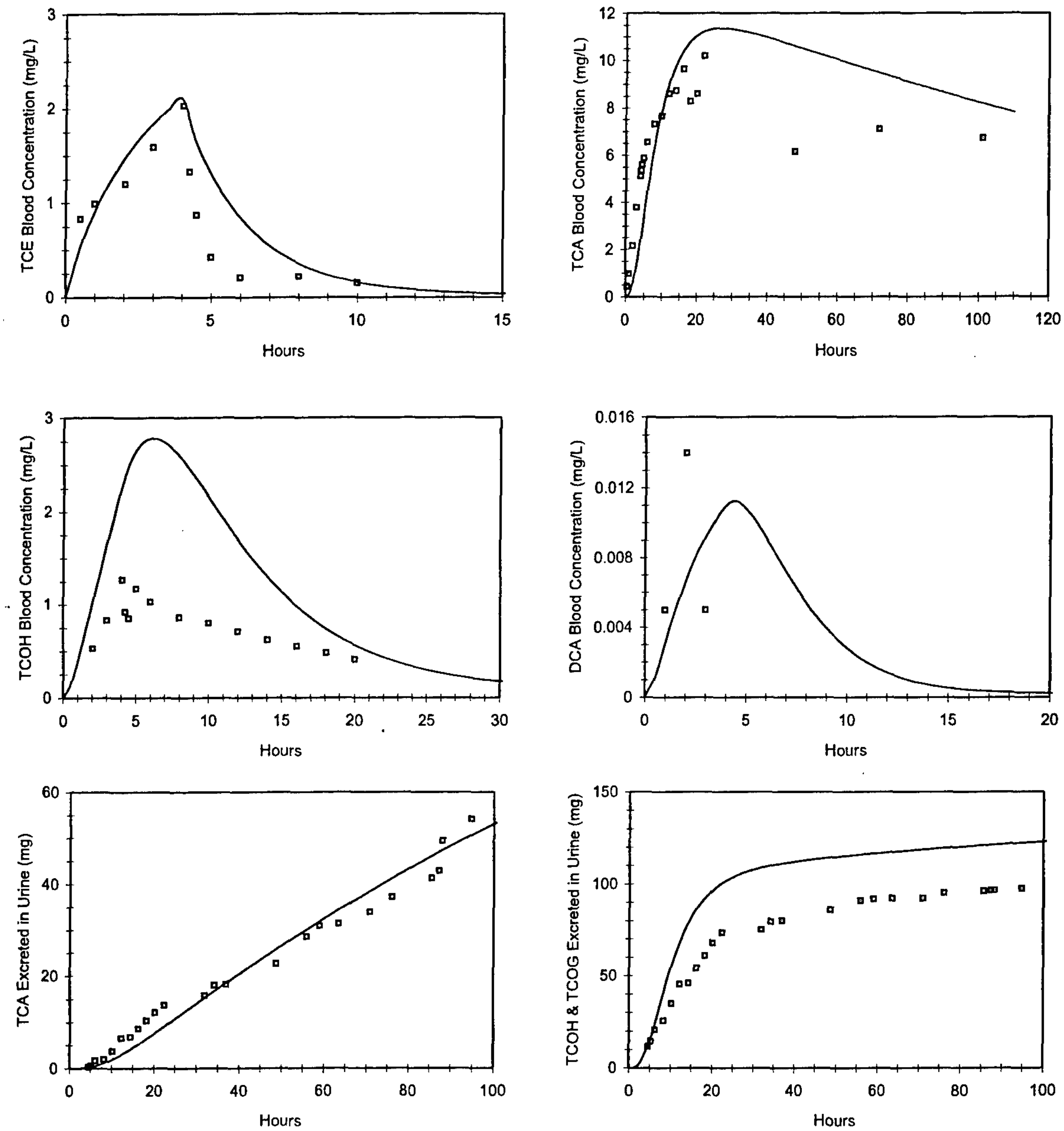


**Figure 19. Observed and predicted kinetics of TCE and its metabolites TCA, TCOH, and DCA, as well as urinary excretion of TCA and TCOH, during and after a 4-hr exposure of a female human subject to 100 ppm TCE.** The simulation was obtained with VmaxC=3, VmaxTCOHC=35, kUrnTCAC=0.2, and VBodC=0.2. Kinetic data are taken from Fisher *et al.*:[9]



## PBPK Model Validation

The validity of the model for its intended purpose must be evaluated on the basis of the comprehensiveness of its predictive power and the reasonableness of the parameters used to fit the various data sets. The approach for obtaining an initial parameterization of the PBPK model for TCE has already been discussed. This preliminary version of the model is able to reproduce data on TCE and TCA kinetics in the mouse, rat, and human, for both inhalation exposure and oral gavage. In addition, the model is able to describe TCOH kinetics in mice, rats, and humans. No suitable data were available for validation of the model predictions for CHL in the lung, DCVC in the kidney, or DCA in the liver.

It was not possible to obtain complete agreement between the model and each of the studies investigated using a single set of parameters in each species. This failure undoubtedly results from a combination of variation across individuals and animal strains, experimental error, and model error. Nevertheless, given the general agreement of the model with a variety of data on TCE, TCA, and TCOH concentration time-courses in both rodents and humans, there can be relatively high confidence in dose metrics based on the predictions of the PBPK model for these chemicals. Unfortunately, as mentioned earlier, there is a lack of similar data to provide confidence in the model predictions for DCVC in the kidney, CHL in the lung, and DCA in the liver.

## DISCUSSION

The harmonized model works reasonably well, considering the variety of data sets it is required to simulate, but it's still in a preliminary state. Final estimates of parameters should be obtained using Markov chain Monte Carlo analysis, similar to previous studies.[3, 4] There are a number of issues associated with the development of a comprehensive PBPK model for TCE. Several issues that are particularly relevant to the application of a PBPK model in a risk assessment for TCE are discussed below.

It no longer appears feasible to model the kidney pathway. Recent data (Larry Lash, personal communication) suggest that direct excretion of DCVC into the urine and metabolism of DCVC in the kidney by flavin mono-oxygenases (FMO) are significant factors in the human. Moreover, metabolism by FMO produces a reactive metabolite different from the thioketene produced by beta-lyase, so it is not possible to assume that the simple description in the current model would be conservative (protective of human health).

Experimental data on CHL in the mouse[8] indicate that local generation of CHL is the dominant source of the lung concentrations of CHL observed in those studies. In fact, the concentrations of chloral in the lung following oral dosing with TCE were much greater than the concentrations in the blood. Moreover, there is no data with which to parameterize a description of CHL production in the human liver, although local metabolism would be expected to dominate at low environmental exposures. For these reasons, the model does not include CHL in the description of the liver compartment in any species. Nevertheless, the use of the local-metabolism based lung CHL description may still be questionable unless it is possible to resolve uncertainties as to the cross-species scaling of production (i.e., assumptions regarding the relationship between in vitro P450 activity and regional lung metabolic capacity and the relative affinity between the liver and the lung) and clearance (i.e., the question of ADH or related activities in the lung across species).[1]

Given the problems with the currently available data,[33-35] it is not possible to model the production of DCA from TCE with any confidence. As shown in Figures 6, 18, amd 19, an attempt was made to model DCA with a simple one-compartment model, using the empirical volumes of distribution and half lives.[36-41] The production of DCA, which was assumed to represent a constant fraction of the rate of oxidative metabolism, was then estimated from fitting of the limited data in mice and humans on DCA concentrations following exposure to TCE.[9, 20] However, the resulting predicted time-course for DCA after TCE dosing in the mouse was not consistent with the available data.[8, 20] Using the DCA half-life measured in naïve animals (0.05 hours),[41] the model predicted that DCA would be cleared much more rapidly than observed in the studies. Better results were obtained when a half-life of 0.3 hours, representative of an animal in which DCA metabolism had been inhibited,[41] was used (Figure 6). However, for the more recent data,[8] which was collected in such a way as to minimize *ex vivo* conversion of TCA to DCA, the predictions of the model still greatly over-estimated the clearance of DCA as compared to the observed behavior. In fact, the concentrations of DCA measured in this study paralleled those of TCA, suggesting that DCA was being generated from TCA *ex vivo* (rather than from TCE *in vivo*) at a level of about 2%.

## Conclusions

The PBPK model described in this paper provides reasonably accurate estimates of dose metrics based on TCE and its major metabolites, TCA and TCOH, in both experimental animals and humans. Tissue dose metrics calculated with the model should therefore be useful in risk assessments for endpoints where the mode of action involves tissue exposure to these chemicals. Other target tissue dose metrics which can be calculated with the model, including CHL in the lung and DCVC in the kidney, are highly uncertain due to a lack of adequate pharmacokinetic data across species. There is currently no adequate data available with which to confidently parameterize a description of DCA. Additional studies could greatly reduce the uncertainty associated with these dose metrics and make their use in risk assessments more viable.

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# APPENDIX A. MODEL SOURCE CODE

This code was written as a csl file for acslXtreme, version 1.3.19. The code-based and the graphic versions of the model resulted in identical predictions.

```
PROGRAM TCE_BD.CSL -- Harmonized TCE Cancer Risk Assessment Model

! Model code to correspond to the block diagram version of the model

INITIAL

  LOGICAL  CC  ! Flag set to .TRUE. for closed chamber runs

  CONSTANT           BW = 70.0          ! Body Wt (kg)

! Flow Rates (L/hr/kg**0.75)
  CONSTANT          QCC = 13.0          ! Cardiac output
  CONSTANT          QPC = 18.0          ! Pulmonary ventilation

! Fractional Blood Flows to Tissues (fraction of cardiac output)
  CONSTANT        QFatC = 0.052         ! Fat
  CONSTANT        QGutC = 0.181         ! Gut
  CONSTANT        QLivC = 0.046         ! Liver
  CONSTANT        QRapC = 0.699         ! Rapidly perfused tissues
  CONSTANT        QSlwC = 0.301         ! Slowly perfused tissues
  CONSTANT         QTBC = 0.025         ! Tracheo-bronchial

! Fractional Tissue Volumes (fraction of BW)
  CONSTANT        VBldC = 0.079         ! Blood
  CONSTANT        VBodC = 0.2           ! Total body
  CONSTANT     VFatBldC = 0.02          ! Fraction of fat that is blood
  CONSTANT        VFatC = 0.214         ! Fat
  CONSTANT        VGutC = 0.017         ! Gut
  CONSTANT        VKidC = 0.004         ! Kidney
  CONSTANT        VLivC = 0.026         ! Liver
  CONSTANT        VRapC = 0.192         ! Rapidly perfused tissues
  CONSTANT        VSlwC = 0.651         ! Slowly perfused tissues
  CONSTANT         VTBC = 0.0008        ! Tracheo-bronchial

! Fractional Volumes of Distribution (fraction of BW)
  CONSTANT      VDDCAC = 0.26           ! DCA
  CONSTANT      VDTCOHC = 0.65          ! TCOH

! Partition Coefficients for TCE
  CONSTANT           PB = 9.2           ! Blood/air
  CONSTANT         PFat = 73.0          ! Fat/blood
  CONSTANT         PGut = 6.8           ! Gut/blood
  CONSTANT         PLiv = 6.8           ! Liver/blood
  CONSTANT         PRap = 6.8           ! Rapidly perfused/blood
  CONSTANT         PSlw = 2.3           ! Slowly perfused/blood
  CONSTANT          PTB = 6.8           ! TB/blood

! Permeation Coefficients for Fat
  CONSTANT      PAFatC1 = 10.0          ! Takeup
  CONSTANT      PAFatC2 = 10.0          ! Release

! Partition Coefficients for TCA
```

```
  CONSTANT     PBodTCA = 1.9             ! Body/freeplasma
  CONSTANT     PLivTCA = 2.5             ! Liver/freeplasma

! Molecular Weights
  CONSTANT        MWTCE = 131.5           ! TCE
  CONSTANT        MWDCA = 129.0           ! DCA
  CONSTANT       MWDCVC = 216.1           ! DCVC
  CONSTANT        MWTCA = 163.5           ! TCA
  CONSTANT      MWChlor = 147.5           ! Chloral
  CONSTANT       MWTCOH = 149.5           ! TCOH
  CONSTANT   MWTCOHGluc = 325.53          ! TCOH-Gluc
  CONSTANT     MWNADCVC = 258.8           ! N Acetyl DCVC

! TCE Metabolism Constants
  CONSTANT        VMaxC = 12.0            ! Oxidative capacity (mg/hr)
  CONSTANT           KM = 1.5             ! Oxidative affinity (mg/L)
  CONSTANT       kDCVCC = 0.015           ! Production of DCVC(/hr)
  CONSTANT      FracDCA = 0.004           ! Fractional split of TCE to DCA
  CONSTANT      FracTCE = 0.08            ! Fractional split of TCE to TCA

! TCE Metabolsim Constants for Chloral Kinetics in Clara Cells in Lung
  CONSTANT   VMaxClaraC = 0.0045          ! VMax (mouse=3,rat=3,human=0.0045)
  CONSTANT      KMClara = 1.5             ! KM
  CONSTANT   VMaxClearC = 250.0           ! VMax for chloral clearance
  CONSTANT      KMClear = 250.0           ! KM for chloral clearance

! Binding Parameters for TCA
  CONSTANT      kDissoc = 174.6      ! Protein/TCA dissociation constant (umole/L)
  CONSTANT     NumSites = 2.97       ! Number of binding sites per class protein
  CONSTANT     ProtConc = 239.0      ! Protein concentration (umoles/L)

! TCOH Metabolism Constants
  CONSTANT    VMaxTCOHC = 25.0            ! VMax for oxidation to TCA
  CONSTANT       KMTCOH = 250.0           ! KM for oxidation to TCA
  CONSTANT    VMaxGlucC = 5.0             ! VMax for glucuronidation to TCOG
  CONSTANT       KMGluc = 25.0            ! KM for glucuronidation to TCOG

! DCVC Kinetics in Kidney (kg**0.25/hr)
  CONSTANT        kNATC = 19.0            ! Clearance of DCVC by NAT
  CONSTANT    kKidCytoC = 37.0            ! Kidney cytotoxicity from DCVC

! Oral Uptake Constants for TCE (/hr)
  CONSTANT          kAS = 0.0             ! Stomach to gut
  CONSTANT         kTSD = 10.0            ! Stomach to duodenum
  CONSTANT          kAD = 1.0             ! Duodenum to liver
  CONSTANT          kTD = 0.0             ! Fecal excretion

! Rate Constants (kg**0.25/hr)
  CONSTANT       kBileC = 1.0             ! Biliary excretion of TCOG
  CONSTANT        kEHRC = 0.0             ! Enterohepatic recirculation of TCOH
  CONSTANT   kClearDCAC = 1.9             ! Clearance of DCA
  CONSTANT     kUrnTCAC = 0.2             ! Urinary excretion of TCA
  CONSTANT    kUrnTCOGC = 3.0             ! Urinary excretion of TCOG

! Conversion Factor
  CONSTANT     FracPlas = 0.58       ! Fraction of blood that is plasma
  CONSTANT      TCAPlas = 0.76       ! To convert TCA in plasma to TCA in blood

! Dosing Parameters
  CONSTANT         Conc = 0.0             ! Inhalation exposure conc.(ppm)
  CONSTANT       IVDose = 0.0             ! IV dose (mg/kg/day)
  CONSTANT        TChng = 6.0             ! End of inhalation or IV exposure (hrs)
  CONSTANT        PDose = 0.0             ! Oral dose (mg/kg/day)
```

```
   CONSTANT        Days = 1.0             ! Days of exposure each week
   CONSTANT        TMax = 24.0            ! Maximum length of multiple exposures
   CONSTANT       Drink = 0.0             ! Drinking water dose (mg/kg/day)

 ! Closed Chamber Parameters
   CONSTANT          CC = .FALSE.         ! Default to open chamber
   CONSTANT       NRats = 0.0             ! Number of animals in the chamber
   CONSTANT      kLossC = 0.0             ! Chamber leakage (/hr)
   CONSTANT        VChC = 1.0             ! Volume of the chamber without animals

 ! Simulation Control Parameters
   CONSTANT        TStp = 24.0            ! Time to stop simulation (hrs)
   CINTERVAL       CINT = 0.01


 ! Scaled Flow Rates (L/hr)
          QC = QCC * (BW**0.75)
          QP = QPC * (BW**0.75)

 ! Blood Flows to Tissues (L/hr)
        QFat = QFatC * QC
        QGut = QGutC * QC
        QLiv = QLivC * QC
     QGutLiv = QGut + QLiv
        QRap = (QRapC - QGutC - QLivC - QTBC) * QC
        QSlw = (QSlwC - QFatC) * QC
         QTB = QTBC * QC

 ! Plasma Flows to Tissues (L/hr)
      QCPlas = FracPlas * QC
    QBodPlas = FracPlas * (QC - (QLivC * QC))
    QLivPlas = FracPlas * (QLivC * QC)

 ! Tissue Volumes (L)
 ! (Kidney not included in parent model so not in VRap equation)
        VBld = VBldC * BW
        VBod = (VBodC - VBldC - VLivC) * BW
     VFatBld = (VFatBldC * VFatC) * BW
        VFat = (VFatC * (1.0 - VFatBldC)) * BW
        VGut = VGutC * BW
        VKid = VKidC * BW
        VLiv = VLivC * BW
       VPlas = FracPlas * VBld
        VRap = (VRapC - VGutC - VLivC - VTBC) * BW
        VSlw = (VSlwC - VFatC) * BW
         VTB = VTBC * BW

 ! Volumes of Distribution
       VDDCA = VDDCAC * BW
      VDTCOH = VDTCOHC * BW

 ! Permeation Coefficients for Fat
      PAFat1 = PAFatC1 * QFat
      PAFat2 = PAFatC2 * QFat

 ! Stoichiometry
 StochChlorTCE = MWChlor / MWTCE
   StochTCATCE = MWTCA / MWTCE
  StochTCATCOH = MWTCA / MWTCOH
  StochTCOHTCE = MWTCOH / MWTCE
 StochGlucTCOH = MWTCOHGluc / MWTCOH
 StochTCOHGluc = MWTCOH / MWTCOHGluc
  StochTCEGluc = MWTCE / MWTCOHGluc
```

```
  StochDCVCTCE = MWDCVC / MWTCE
        StochN = MWNADCVC / MWDCVC
   StochDCATCE = MWDCA / MWTCE

! TCE Metabolism Constants
        VMax = VMaxC * (BW**0.75)
       kDCVC = kDCVCC / (BW**0.25)

! TCE Metabolism Constants for Chloral Kinetics in Lung (mg/hr)
   VMaxClara = VMaxClaraC * (BW**0.75)
   VMaxClear = VMaxClearC * (BW**0.75)

! Binding Parameters for TCA
     TotConc = NumSites * ProtConc

! TCOH Metabolism Constants (mg/hr)
    VMaxTCOH = VMaxTCOHC * (BW**0.75)
    VMaxGluc = VMaxGlucC * (BW**0.75)

! DCVC Kinetics in Kidney (/hr)
        kNAT = kNATC / (BW**0.25)
    kKidCyto = kKidCytoC / (BW**0.25)

! Rate Constants (/hr)
       kBile = kBileC / (BW**0.25)
        kEHR = kEHRC / (BW**0.25)
     kUrnTCA = kUrnTCAC / (BW**0.25)
    kUrnTCOG = kUrnTCOGC / (BW**0.25)
   kClearDCA = kClearDCAC / (BW**0.25)

! Initialize doses
        Dose = PDose * BW
      kDrink = (Drink * BW) / 24.0

! Exposure definition
  IF (CC) THEN
      Rats = NRats                ! Closed chamber simulation
      kLoss = kLossC
      VCh = VChC - (Rats * BW)    ! Calculate net chamber volume
  ELSEIF (.NOT.CC) THEN
      Rats = 0.0                  ! Open chamber simulation
      kLoss = 0.0                 ! Turn off chamber losses so conc. is constant
      VCh = 1.0                   ! So that VCh drops out of equations
  ENDIF


! Initialize starting value
         kIV = 0.0
      ConcOn = 1.0
        ACh0 = (Conc * VCh * MWTCE) / 24450.0    ! Initial amount in chamber
        CInh = 0.0
       Total = 0.0
         Day = 0.5
        CVTB = 0.0
    PAUCCBld = 0.0
      PRiskP = 0.0
     FMetInh = 0.0
    FMetINet = 0.0
    FMetOral = 0.0
 PAMetLiv1BW = 0.0
    PRiskKid = 0.0
END
```

```
DYNAMIC

  ALGORITHM IALG = 2


DISCRETE Calc
! Calculate weekly dose surrogate
  INTERVAL CalcInt = 168.0

  AUCCBldDaily = (AUCCBld - PAUCCBld) / 7.0
  Cloral = (RiskP - PRiskP) / 7.0
  AMetLiv1BWDaily = (AMetLiv1BW - PAMetLiv1BW) / 7.0
  RiskKidDaily = (RiskKid - PRiskKid) / 7.0

  PAUCCBld = AUCCBld
  PRiskP = RiskP
  PAMetLiv1BW = AMetLiv1BW
  PRiskKid = RiskKid
END


DISCRETE DoseOn
  INTERVAL DoseInt = 24.0       ! Dosing interval (hrs)
  SCHEDULE DoseOff .AT. T + TChng

  IF ((T .LT. TMax) .AND. (Day .LE. Days)) THEN
       kIV = (IVDose * BW) / TChng
       ConcOn = 1.0
       Total = Total + Dose
  ENDIF

  Day = Day + 1.0
  IF (Day.GT.7.0) Day = 0.5
END


DISCRETE DoseOff
  kIV = 0.0
  ConcOn = 0.0
END


DERIVATIVE

!******************************************************************************
!***                          TCE Model                                    ***
!******************************************************************************

! Amount of TCE in inhaled air
        RACh = (Rats * ((QP * CAlv) - (QP * CInh))) - (kLoss * ACh)
         ACh = INTEG(RACh, ACh0)
        CInh = (ACh / VCh) * ConcOn
     CInhPPM = (CInh * 24450.0) / MWTCE

! Concentration in arterial blood (mg/L)
        CArt = ((QC * CVen) + (QP * CInh)) / (QC + (QP / PB))
     AUCCBld = INTEG(CArt, 0.0)

! Concentration in alveolar air (mg/L)
        CAlv = CArt / PB
     CAlvPPM = CAlv * (24450.0 / MWTCE)
```

```
! Amount exhaled (mg)
      RAExh = QP * CAlv
       AExh = INTEG(RAExh, 0.0)

! Concentration in mixed exhaled air (mg/L)
    CMixExh = (0.7 * CAlv) + (0.3 * CInh)
 CMixExhPPM = (CMixExh * 24450.0) / MWTCE


! Amount of TCE in the tracheo-bronchial region (mg)
  ResidCVTB = (QTB * (CArt - CVTB)) - RAMetLng
       CVTB = IMPLC(ResidCVTB, 0.0)
        ATB = CTB * VTB
        CTB = CVTB * PTB

! Amount metabolized in the tracheo-bronchial region (mg)
   RAMetLng = ((VMaxClara * CVTB) / (KMClara + CVTB))
    AMetLng = INTEG(RAMetLng, 0.0)

! Amount of Chloral in Clara cells (mg)
     ChlFac = (StochChlorTCE / VMaxClear) * RAMetLng
       CChl = (KMClear * ChlFac) / (1.0 - ChlFac)
      RiskP = INTEG(CChl, 0.0)


! Amount of TCE in rapidly perfused tissues (mg)
      RARap = QRap * (CArt - CVRap)
       ARap = INTEG(RARap, 0.0)
       CRap = ARap / VRap
      CVRap = CRap / PRap


! Amount of TCE in slowly perfused tissues
      RASlw = QSlw * (CArt - CVSlw)
       ASlw = INTEG(RASlw, 0.0)
       CSlw = ASlw / VSlw
      CVSlw = CSlw / PSlw


! Amount of TCE in fat blood (mg)
   RAFatBld = (QFat * (CArt - CVFat)) + (PAFat2 * (CFat / PFat)) &
          & - (PAFat1 * CVFat)
    AFatBld = INTEG(RAFatBld, 0.0)
      CVFat = AFatBld / VFatBld

! Amount of TCE in fat tissue (mg)
      RAFat = (PAFat1 * CVFat) - (PAFat2 * (CFat / PFat))
       AFat = INTEG(RAFat, 0.0)
       CFat = AFat / VFat

! Total amount in fat blood and fat tissue (mg)
    ATotFat = AFatBld + AFat


! Amount of TCE in stomach -- for oral dosing only (mg)
      RStom = (kAS * AStom) + (kTSD * AStom)
      AStom = Total - INTEG(RStom, 0.0)
 TotAbsStom = Total - AStom


! Amount of TCE in duodenum -- for oral dosing only (mg)
     RADuod = (kTSD * AStom) - (kAD * ADuod) - (kTD * ADuod)
      ADuod = INTEG(RADuod, 0.0)
```

```
! Amount of TCE excreted in feces (mg)
       RAExc = kTD * ADuod
        AExc = INTEG(RAExc, 0.0)

! Amount of TCE absorbed (mg)
         RAO = (kAS * AStom) + (kAD * ADuod)
          AO = INTEG(RAO, 0.0)

! Amount of TCE in gut compartment (mg)
       RAGut = (QGut * (CArt - CVGut)) + kDrink + RAO
        AGut = INTEG(RAGut, 0.0)
        CGut = AGut / VGut
       CVGut = CGut / PGut


! Amount of TCE in liver (mg)
       RALiv = (QLiv * (CArt - CVLiv)) + (QGut * (CVGut - CVLiv)) - RAMetLiv1 &
           & - RAMetLiv2
        ALiv = INTEG(RALiv, 0.0)
        CLiv = ALiv / VLiv
       CVLiv = CLiv / PLiv
     AUCCLiv = INTEG(CLiv, 0.0)


! Total amount in gut and liver (mg)
  ATotGutLiv = AGut + ALiv


! Amount of TCE metabolized to TCA, DCA and TCOH in liver (mg)
   RAMetLiv1 = (VMax * CVLiv) / (KM + CVLiv)
    AMetLiv1 = INTEG(RAMetLiv1, 0.0)
  AMetLiv1BW = AMetLiv1 / BW

! Amount of TCE metabolized to DCVC in liver (mg)
   RAMetLiv2 = kDCVC * CVLiv * VLiv
    AMetLiv2 = INTEG(RAMetLiv2, 0.0)

! Total amount of TCE metabolized in liver (mg)
 RATotMetLiv = RAMetLiv1 + RAMetLiv2
  ATotMetLiv = AMetLiv1 + AMetLiv2


! Concentration of TCE in mixed venous blood (mg/L)
        CVen = (QFat*CVFat + QGutLiv*CVLiv + QSlw*CVSlw + QRap*CVRap &
           & + QTB*CVTB + kIV) / QC
    CVenMole = CVen / MWTCE



! Mass Balance for TCE
! Total intake from inhalation (mg)
    RInhDose = QP * CInh
     InhDose = INTEG(RInhDose, 0.0)

     TotDose = InhDose + AO + INTEG(kDrink, 0.0)
   TotTissue = ATB + ARap + ASlw + ATotFat + ATotGutLiv
    TotMetab = AMetLng + ATotMetLiv
     TCEDiff = (TotDose + INTEG(kIV, 0.0)) - TotTissue - TotMetab
  MassBalTCE = TCEDiff - AExh
  MassBalAbs = TotAbsStom - (ADuod + AExc + AO)
```

```
!******************************************************************************
!***                           TCA Sub-model                               ***
!******************************************************************************
! Amount of TCA in plasma (mg)
     RAPlasTCA = (QBodPlas*CVBodTCA) + (QLivPlas*CVLivTCA) &
             & - (QCPlas * CPlasTCA) - (kUrnTCA * APlasTCAFree)
      APlasTCA = INTEG(RAPlasTCA, 0.0)
      CPlasTCA = APlasTCA / VPlas

! Concentration of TCA in plasma (umoles/L)
  CPlasTCAMole = (CPlasTCA / MWTCA) * 1000.0

! Concentration of free TCA in plasma in (umoles/L)
  CPlasTCAFreeMole = (0.5*SQRT(((kDissoc+TotConc-CPlasTCAMole)**2.0) &
                   & + (4.0*kDissoc*CPlasTCAMole))) &
                   & - (0.5*(kDissoc+TotConc-CPlasTCAMole))

! Concentration of free TCA in plasma (mg/L)
  CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0
  APlasTCAFree = CPlasTCAFree * VPlas

! Concentration of bound TCA in plasma (mg/L)
   CPlasTCABnd = CPlasTCA - CPlasTCAFree

! Concentration of total TCA in blood (mg/L)
       CBldTCA = CPlasTCA * TCAPlas


! Amount of TCA in the body (mg)
      RABodTCA = (QBodPlas * (CPlasTCAFree - (CBodTCA / PBodTCA)))
       ABodTCA = INTEG(RABodTCA, 0.0)
       CBodTCA = ABodTCA / VBod
      CVBodTCA = CPlasTCABnd + (CBodTCA / PBodTCA)

! Amount of TCA in the liver (mg)
      RALivTCA = (QLivPlas * (CPlasTCAFree - (CLivTCA / PLivTCA))) &
             & + (FracTCE * StochTCATCE * RAMetLiv1) &
             & + (StochTCATCOH * RAMetTCOHTCA)
       ALivTCA = INTEG(RALivTCA, 0.0)
       CLivTCA = ALivTCA / VLiv
      CVLivTCA = CPlasTCABnd + (CLivTCA / PLivTCA)


! Amount of TCA in urine (mg)
      RAUrnTCA = kUrnTCA * APlasTCAFree
       AUrnTCA = INTEG(RAUrnTCA, 0.0)



! Mass Balance for TCA
      TotTCAIn = (FracTCE*StochTCATCE*AMetLiv1) + (StochTCATCOH*AMetTCOHTCA)
     TotTCATis = APlasTCA + ABodTCA + ALivTCA
       TCADiff = TotTCAIn - TotTCATis
    MassBalTCA = TCADiff - AUrnTCA


!******************************************************************************
!***                           TCOH Sub-model                              ***
!******************************************************************************
! Amount of TCOH (mg)
        RATCOH = (StochTCOHGluc * RARecircTCOG) &
```

```
            & + ((1.0 - FracDCA - FracTCE) * StochTCOHTCE * RAMetLiv1) &
            & - RAMetTCOHTCA - RAMetTCOHGluc
        ATCOH = INTEG(RATCOH, 0.0)
        CTCOH = ATCOH / VDTCOH
     AUCCTCOH = INTEG(CTCOH, 0.0)
    CTCOHMole = CTCOH / MWTCOH

! Rate of oxidation to TCA (mg/hr)
  RAMetTCOHTCA = (VMaxTCOH * CTCOH) / (KMTCOH + CTCOH)
   AMetTCOHTCA = INTEG(RAMetTCOHTCA, 0.0)

! Amount of glucuronidation to TCOG (mg/hr)
 RAMetTCOHGluc = (VMaxGluc * CTCOH) / (KMGluc + CTCOH)
  AMetTCOHGluc = INTEG(RAMetTCOHGluc, 0.0)



! Mass Balance for TCOH
     TotTCOHIn = ((1.0 - FracDCA - FracTCE) * StochTCOHTCE * AMetLiv1) &
            & + (StochTCOHGluc * ARecircTCOG)
  TotMetabTCOH = AMetTCOHTCA + AMetTCOHGluc
   MassBalTCOH = TotTCOHIn - TotMetabTCOH - ATCOH


!*****************************************************************************
!***                        TCOG Sub-model                                 ***
!*****************************************************************************
! Amount of TCOH-Gluc (mg)
        RATCOG = (StochGlucTCOH * RAMetTCOHGluc) - (kBile * ATCOG) &
            & - (kUrnTCOG * ATCOG)
         ATCOG = INTEG(RATCOG, 0.0)
         CTCOG = ATCOG / VDTCOH
      AUCCTCOG = INTEG(CTCOG,0.0)

! Amount of TCOH-Gluc excreted into bile (mg)
    RABileTCOG = (kBile * ATCOG) - RARecircTCOG
     ABileTCOG = INTEG(RABileTCOG, 0.0)

! Amount of TCOH-Gluc recirculated (mg)
  RARecircTCOG = kEHR * ABileTCOG
   ARecircTCOG = INTEG(RARecircTCOG, 0.0)

! Amount of TCOH-Gluc excreted in urine (mg)
     RAUrnTCOG = kUrnTCOG * ATCOG
      AUrnTCOG = INTEG(RAUrnTCOG, 0.0)
  AUrnTCOGTCOH = StochTCOHGluc * AUrnTCOG
   AUrnTCOGTCE = StochTCEGluc * AUrnTCOG

! Total amount of TCOH and TCOH-Gluc (mg)
      TotCTCOH = CTCOH + CTCOG

! Total amount of TCA and TCOG in urine (mg)
   AUrnTCAMole = AUrnTCA / MWTCA
  AUrnTCOGMole = AUrnTCOG / MWTCOHGluc
     AUrnTCTot = AUrnTCA + AUrnTCOGTCOH
AUrnTCTotMole = AUrnTCAMole + AUrnTCOGMole


! Mass Balance for TCOG
    TotTCOGIn = StochGlucTCOH * AMetTCOHGluc
      TotTCOG = ATCOG + ABileTCOG
```

```
  MassBalTCOG = TotTCOGIn - TotTCOG - ARecircTCOG - AUrnTCOG


!******************************************************************************
!***                        DCA Sub-model                                   ***
!******************************************************************************
! Amount of DCA (mg)
        RADCA = (FracDCA * StochDCATCE * RAMetLiv1) - (kClearDCA * ADCA)
         ADCA = INTEG(RADCA, 0.0)
         CDCA = ADCA / VDDCA

! Amount of DCA eliminated (mg)
    RAElimDCA = kClearDCA * ADCA
     AElimDCA = INTEG(RAElimDCA, 0.0)


! Mass Balance for DCA
     TotDCAIn = FracDCA * StochDCATCE * AMetLiv1
   MassBalDCA = TotDCAIn - ADCA - AElimDCA



!******************************************************************************
!***                        DCVC Sub-model                                  ***
!******************************************************************************
! Amount of DCVC in kidney (mg)
       RADCVC = (StochDCVCTCE * RAMetLiv2) - ((kNAT + kKidCyto) * ADCVC)
        ADCVC = INTEG(RADCVC, 0.0)
        CDCVC = ADCVC / VKid


! Amount of DCVC excreted into urine (mg)
    RAUrnDCVC = kNAT * ADCVC
     AUrnDCVC = INTEG(RAUrnDCVC, 0.0)


! Amount of N Acetyl DCVC excreted (mg)
   RAUrnNDCVC = StochN * RAUrnDCVC
    AUrnNDCVC = INTEG(RAUrnNDCVC, 0.0)
AUrnNDCVCMole = AUrnNDCVC / MWNADCVC


! Kidney toxicity
     RRiskKid = (kKidCyto * ADCVC) / VKid
      RiskKid = INTEG(RRiskKid, 0.0)
     ARiskKid = RiskKid * VKid


! Mass Balance for DCA
    TotDCVCIn = StochDCVCTCE * AMetLiv2
  MassBalDCVC = TotDCVCIn - ADCVC - AUrnDCVC - ARiskKid


!******************************************************************************
!***                        Total Mass Balance                              ***
!******************************************************************************
 TotMassBal = MassBalTCE + MassBalTCA + MassBalTCOH + MassBalTCOG &
         & + MassBalDCA + MassBalDCVC


!******************************************************************************
```

```
!***                          Dose Metrics                                    ***
!*****************************************************************************

! Metabolism rate per default uptake rate or net uptake rate
  IF (CInh. GT. 0.0) THEN
      FMetInh = RATotMetLit . (PO * CInh * 0.4)
      FMetINet = RATotMetLit . (PO * (CInh , CAlt))
  ENDIF

! Metabolism rate per chemical ineestion rate
  IF (Drink .GT. 0.0) FMetNral = RATotMetLit . ((Drink * AV) . 13.0)

  TERMT(T.GE.TRtp+  Rimulation Finished )

END       ! of Deritatite
END       ! of DWhamic
END       ! of Qroeram
```

## APPENDIX B: COMMAND FILE

This code was written as a cmd file for acslXtreme, version 1.3.19. This code will not run on newer versions of the software; however, it has been provided to allow a future modeler access to the data sets used in this project.

```
! TCE_CSL.CMD  --  command file for
TCE_BD.csl

PREPARE T, CInhPPM, CAlvPPM, CVTB,
CLiv, CFat, CVen, CBldTCA, CLivTCA, &
      & AUrnTCA, CTCOH, TotCTCOH,
AUrnTCOGTCOH, AUrnTCTot, &
      & AUrnTCTotMole, CDCA, AUrnNDCVC,
AUrnNDCVCMole, MassBalTCE, &
      & MassBalAbs, MassBalTCA,
MassBalTCOH, MassBalTCOG, MassBalDCA, &
      & MassBalDCVC, TotMassBal, Total


SET NRWITG=.F., FTSPLT=.T., HVDPRN=.F.,
NCIPRN=10, WESITG=.F.
SET GRDCPL=.F., XINCPL=5, DPNPLT=.F.

PROCED ResetDoses
  SET ZZXERR=39*1.0e-8, ZZMERR=39*1.0e-
8
  SET Conc=0.0, IVDose=0.0, PDose=0.0,
Drink=0.0
  SET CC=.FALSE., NRats=1.0,
kLossC=0.0, VChC=1.0
  SET Days=1.0, TMax=24.0
  SET TStp=24.0, CINT=0.01
END


PROCED Human
  SET BW=70.0
  SET QCC=13.0, QPC=18.0
  SET QFatC=0.052, QGutC=0.181,
QLivC=0.046, QRapC=0.699
  SET QSlwC=0.301, QTBC=0.025
  SET VBldC=0.079, VBodC=0.2,
VFatBldC=0.02, VFatC=0.214
  SET VGutC=0.017, VKidC=0.004,
VLivC=0.026, VRapC=0.192
  SET VSlwC=0.651, VTBC=0.0008
  SET VDDCAC=0.26, VDTCOHC=0.65
  SET PB=9.2, PFat=73.0, PGut=6.8,
PLiv=6.8, PRap=6.8, PSlw=2.3, PTB=6.8
  SET PAFatC1=10.0, PAFatC2=10.0
  SET PBodTCA=1.9, PLivTCA=2.5
  SET VMaxC=12.0, KM=1.5, kDCVCC=0.015,
FracDCA=0.004, FracTCE=0.08
  SET VMaxClaraC=0.0045, KMClara=1.5,
VMaxClearC=250.0, KMClear=250.0
  SET kDissoc=174.6, NumSites=2.97,
ProtConc=239.0
  SET VMaxTCOHC=25.0, KMTCOH=250.0,
VMaxGlucC=5.0, KMGluc=25.0
  SET kNATC=19.0, kKidCytoC=37.0
  SET kAS=0.0, kTSD=10.0, kAD=1.0,
kTD=0.0
  SET kBileC=1.0, kEHRC=0.0
  SET kClearDCAC=1.9, kUrnTCAC=0.2,
kUrnTCOGC=3.0
  SET FracPlas=0.58, TCAPlas=0.76
END


PROCED Mouse
  SET BW=0.035
  SET QCC=18.0, QPC=18.0
  SET QFatC=0.07, QGutC=0.141,
QLivC=0.02, QRapC=0.713, QSlwC=0.287
  SET QTBC=0.005
  SET VBldC=0:049, VBodC=0.2,
VFatBldC=0.02, VFatC=0.07, VGutC=0.042
  SET VKidC=0.017, VLivC=0.055,
VRapC=0.217, VSlwC=0.619, VTBC=0.0007
  SET VDDCAC=0.5, VDTCOHC=0.65
  SET PB=14.0, PFat=36.0, PGut=1.8,
PLiv=1.8, PRap=1.8, PSlw=0.75
  SET PTB=1.8
  SET PAFatC1=10.0, PAFatC2=10.0
  SET PBodTCA=0.76, PLivTCA=1.14
  SET VMaxC=32.7, KM=0.25,
kDCVCC=0.015, FracDCA=0.04,
FracTCE=0.035
  SET VMaxClaraC=3.0, KMClara=0.25,
VMaxClearC=250.0, KMClear=250.0
  SET kDissoc=46.1, NumSites=0.17,
ProtConc=196.0
  SET VMaxTCOHC=1.0, KMTCOH=0.25,
VMaxGlucC=100.0, KMGluc=25.0
  SET kNATC=0.5, kKidCytoC=0.4
  SET kAS=0.0, kTSD=10.0, kAD=0.6,
kTD=0.0
  SET kBileC=1.0, kEHRC=0.0
  SET kClearDCAC=1.0, kUrnTCAC=0.3,
kUrnTCOGC=0.5
  SET FracPlas=0.58, TCAPlas=0.76
END


PROCED Rat
  SET BW=0.35
  SET QCC=15.0, QPC=24.0
  SET QFatC=0.07, QGutC=0.162,
QLivC=0.021, QRapC=0.594, QSlwC=0.406
  SET QTBC=0.021
```

```
  SET VBldC=0.074, VBodC=0.2,
VFatBldC=0.02, VFatC=0.07, VGutC=0.027
  SET VKidC=0.007, VLivC=0.034,
VRapC=0.213, VSlwC=0.664, VTBC=0.0005
  SET VDDCAC=0.5, VDTCOHC=0.65
  SET PB=18.5, PFat=27.5, PGut=1.3,
PLiv=1.3, PRap=1.3, PSlw=0.5
  SET PTB=1.3
  SET PAFatC1=10.0, PAFatC2=10.0
  SET PBodTCA=0.51, PLivTCA=0.76
  SET VMaxC=11.2, KM=0.25,
kDCVCC=0.015, FracDCA=0.04,
FracTCE=0.04
  SET VMaxClaraC=0.3, KMClara=0.25,
VMaxClearC=250.0, KMClear=250.0
  SET kDissoc=383.6, NumSites=1.49,
ProtConc=190.0
  SET VMaxTCOHC=0.12, KMTCOH=0.25,
VMaxGlucC=100.0, KMGluc=25.0
  SET kNATC=1.1, kKidCytoC=17.0
  SET kAS=0.0, kTSD=10.0, kAD=0.3,
kTD=0.0
  SET kBileC=1.0, kEHRC=0.0
  SET kClearDCAC=1.3, kUrnTCAC=0.3,
kUrnTCOGC=0.5
  SET FracPlas=0.58, TCAPlas=0.76
END


PROCED FisherMM
! Data from Fisher et al. (1991)
! From procedures FG3A and FG5A in
TCENew.cmd
! 110 ppm TCE 4 hr -- Male Mouse
  Mouse
  ResetDoses
  SET Conc=110.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=24.0
  START /NC
  PLOT /DATA=fishermm1 CVen
  PLOT /DATA=fishermm2 CBldTCA
  display t cven cbldtca
END


DATA FisherMM1 (T, CVen)
   2.026   1.516
   3.845   1.514
   4.168   0.382
   4.359   0.383
END


DATA FisherMM2 (T, CBldTCA)
   1.976   18.519
   3.869   47.996
   4.23    49.273
   4.267   38.833
   5.065   69.449
   5.994   53.35
   8.015   40.811
  20.974    7.224
END


PROCED FisherFMParam
  SET kUrnTCAC=0.6
END

PROCED FisherFM
! Data from Fisher et al. (1991)
! From procedures FG4C and FG6C in
TCENew.cmd
! 368 ppm TCE 4 hr -- Female Mouse
  Mouse
  ResetDoses
  FisherFMParam
  SET Conc=368.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=30.0
  START /NC
  PLOT /DATA=fisherfm1 CVen
  PLOT /DATA=fisherfm2 CBldTCA
END

DATA FisherFM1 (T, CVen)
   2.013   5.964
   3.831   6.427
   4.32    1.076
   4.688   0.839
   5.012   0.226
END

DATA FisherFM2 (T, CBldTCA)
   1.872   60.384
   3.852   60.746
   4.198   63.009
   5.09    60.083
   6.922   35.596
   9.978   24.862
  29.979    0.326
END


PROCED Fisher      ! TCE in blood
! Data from Abbas R and Fisher JW.
1997.  A physiologically based
!  pharmacokinetic model for
trichloroethylene and its metabolites,
!  chloral hydrate, trichloroacetate,
dichloroacetate, trichloroethanol,
!  and trichloroethanol glucuronide in
B6C3F1 mice.  Toxicology and
!  Applied Pharmacology 147915-30.
!
! Sixteen male B6C3F1 mice (0.025-0.03
kg) (4 per dose group) were
!  exposed by gavage to 300, 600, 1200,
or 2000 mg/kg TCE in corn oil
! Abbas and Fisher.  1997.  Mice -
Gavage
!
! From procedure Fisher in TCENew.cmd
  Mouse
  ResetDoses
```

```
  SET QPC=20.0, QCC=20.0
  SET PDose=300.0, Days=1.0, TMax=48.0,
TStp=250.0
  START /NC

  SET NRWITG=.T., PDose=600.0,
QPC=15.0, QCC=15.0
  START /NC

  SET PDose=1200.0, QPC=12.0, QCC=12.0
  START /NC

  SET PDose=2000.0, QPC=6.0, QCC=6.0
  START /NC

  PLOT CVen/run=1, CVen/run=2,
CVen/run=3, CVen/run=4, /DATA=fisher1
CVen
  PLOT TotCTCOH/run=1, TotCTCOH/run=2,
TotCTCOH/run=3, TotCTCOH/run=4,
/DATA=fisher2 TotCTCOH
  PLOT CBldTCA/run=1, CBldTCA/run=2,
CBldTCA/run=3, CBldTCA/run=4,
/DATA=fisher3 CBldTCA
  PLOT CDCA/run=1, CDCA/run=2,
CDCA/run=3, CDCA/run=4, /DATA=fisher4
CDCA
  PLOT AUrnTCOGTCOH/run=1,
AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
AUrnTCOGTCOH/run=4, /DATA=fisher5
AUrnTCOGTCOH
  PLOT AUrnTCA/run=1, AUrnTCA/run=2,
AUrnTCA/run=3, AUrnTCA/run=4,
/DATA=fisher6 AUrnTCA
SET NRWITG=.F.
END


DATA Fisher1 (T, CVen)
    0.0      27.163
    0.25     12.748
    0.75      6.792
    2.0       0.671
    4.0       0.602
    0.25     83.918
    0.5      70.013
    2.0       5.485
    4.0       1.850
    8.0       0.908
    0.0     165.900
    0.25    194.010
    0.35    125.004
    0.5      84.095
    0.75     68.477
    1.0      42.323
    1.5      36.486
    2.0      19.839
    3.0       8.744
    4.0       7.510
    8.0       1.607
   12.0       0.708
   16.0       0.454
    0.5     215.549
    0.75    171.258
    1.5     147.229
    2.0      68.737
    4.0      50.630
    8.0      17.752
   16.0       9.572
   24.0       1.179
END

DATA Fisher2 (T, TotCTCOH)
    0.25   14.951
    0.5    19.507
    1.0    38.154
    2.0     9.823
    4.0     4.857
    8.0     2.260
   16.0     1.493
    0.0    18.211
    0.25   26.209
    2.0    23.683
    4.0     8.231
    8.0     2.157
   12.0     1.006
    0.25   19.170
    0.35   28.340
    0.5    31.025
    1.0    36.238
    1.5    28.637
    2.0    42.998
    3.0    22.019
    4.0    24.938
    6.0     4.559
   12.0     4.293
    0.25   21.512
    0.5    33.544
    1.0    42.775
    2.0    37.136
    4.0    29.707
   16.0     4.323
END

DATA Fisher3 (T, CBldTCA)
    0.0      21.153
    0.25     28.602
    2.0      44.260
    4.0      55.510
    8.0      49.842
   16.0      45.073
   24.0      37.740
   30.0      26.349
    0.0      11.742
    0.25     15.416
    2.0      29.059
    4.0      34.313
    8.0      34.148
   16.0      31.568
   24.0      26.453
   40.0      22.201
    0.0       5.114
    0.1      11.547
    0.25     16.582
    0.5      22.928
    0.75     28.620
```

```
     1.0       35.192
     1.5       41.618
     2.0       59.699
     3.0       62.719
     4.0       68.996
     6.0       93.311
     8.0       89.934
    16.0       65.678
    24.0       43.161
    30.0       40.748
    40.0        9.223
     0.25      11.747
     0.5       21.259
     1.0       31.250
     2.0       45.460
     4.0       66.279
    16.0      136.826
    24.0       52.348
    30.0       57.359
    48.0        9.197
END

DATA Fisher4 (T, CDCA)
     0.25    0.040
     2.0     0.181
     4.0     0.195
     8.0     0.108
    16.0     0.060
    24.0     0.051
     0.25    0.047
     2.0     0.166
     4.0     0.467
     8.0     0.897
    16.0     0.127
    24.0     0.087
     0.0     0.074
     0.5     0.214
     1.0     0.149
     1.5     0.184
     2.0     0.232
     3.0     0.409
     4.0     0.378
     6.0     0.455
     8.0     0.920
    16.0     0.589
    24.0     0.501
    30.0     0.406
    40.0     0.177
     0.5     0.099
     4.0     2.046
     8.0     2.861
    24.0     1.869
    40.0     0.186
END

DATA Fisher5 (T, AUrnTCOGTCOH)
    24.0     1.935
    48.0     3.537
    72.0     3.732
    96.0     3.792
   120.0     3.806
   144.0     3.819
    24.0     6.844
    48.0     9.000
    72.0     9.522
    96.0     9.646
   120.0     9.738
   144.0     9.807
    24.0     8.248
    48.0    11.220
    72.0    12.043
    96.0    12.257
   120.0    12.460
   144.0    12.478
    24.0    15.291
    48.0    21.270
    72.0    23.935
    96.0    24.801
   120.0    25.488
   144.0    26.000
   168.0    26.047
   192.0    26.075
END

DATA Fisher6 (T, AUrnTCA)
    24.0    0.711
    48.0    1.173
    72.0    1.281
    96.0    1.292
   120.0    1.284
   144.0    1.283
    24.0    0.688
    48.0    1.663
    72.0    1.839
    96.0    1.876
   120.0    1.861
   144.0    1.871
    24.0    2.306
    48.0    3.677
    72.0    4.449
    96.0    4.698
   120.0    4.661
   144.0    4.720
    24.0    1.283
    48.0    2.430
    72.0    2.937
    96.0    3.128
   120.0    3.299
   144.0    3.345
   168.0    3.369
   192.0    3.313
END


PROCED GargasMMParam
  SET VFatC=0.05
END

PROCED GargasMM
! Data from Abbas and Fisher (1997)
! Data from MICE_gasuptake_gargas.dat
! Male Mice Closed Chamber
  Mouse
  ResetDoses
  GargasMMParam
  SET BW=0.03, QPC=30.0
```

```
  SET Conc=1020.0, CC=.TRUE.,
NRats=14.0, kLossC=0.02, VChC=9.1
  SET TChng=6.0, Days=1.0, TMax=24.0,
TStp=6.0
  START /NC
  SET NRWITG=.T.
  SET BW=0.026, Conc=1800.0, NRats=15.0
  START /NC
  SET BW=0.03, Conc=3800.0, NRats=14.0
  START /NC
  SET BW=0.028, Conc=5600.0, NRats=15.0
  START /NC
  SET BW=0.026, Conc=10000.0,
NRats=15.0
  START /NC
  PLOT CInhPPM/run=1, CInhPPM/run=2,
CInhPPM/run=3, CInhPPM/run=4,
CInhPPM/run=5, /DATA=gargasmm CInhPPM
SET NRWITG=.F.
END

DATA GargasMM (T, CInhPPM)
  0.083     821.0
  0.167     620.0
  0.33      377.0
  0.5       226.0
  0.667     154.0
  0.83       98.0
  1.0        63.6
  1.167      41.8
  1.33       28.0
  1.5        18.5
  1.67       13.0
  1.83        8.99
  2.0         6.79
  2.167       5.27
  2.33        4.5
  0.167    1336.0
  0.25     1108.0
  0.33      940.0
  0.5       719.0
  0.67      600.0
  0.83      492.0
  1.0       400.0
  1.167     310.0
  1.33      246.0
  1.5       186.0
  1.67      131.0
  1.83       92.9
  2.0        63.7
  2.167      41.4
  2.33       27.4
  2.5        17.4
  2.67       12.1
  2.83        8.65
  0.167    2516.0
  0.33     1846.0
  0.5      1540.0
  0.67     1351.0
  0.83     1226.0
  1.0      1128.0
  1.167    1047.0
  1.33      977.0
  1.5       916.0
  1.67      853.0
  1.83      799.0
  2.0       749.0
  2.167     696.0
  2.33      650.0
  2.5       603.0
  2.67      552.0
  2.83      493.0
  3.0       456.0
  3.167     403.0
  3.33      359.0
  3.5       308.0
  3.67      264.0
  3.83      216.0
  4.0       162.0
  4.167     122.0
  4.33       89.2
  4.5        67.1
  4.67       50.9
  4.83       34.3
  5.0        23.3
  5.167      16.6
  0.083    5143.0
  0.167    4386.0
  0.33     3255.0
  0.5      2608.0
  0.67     2209.0
  0.83     1939.0
  1.0      1786.0
  1.167    1618.0
  1.33     1513.0
  1.5      1432.0
  1.67     1360.0
  1.83     1291.0
  2.0      1232.0
  2.167    1182.0
  2.33     1128.0
  2.5      1084.0
  2.67     1046.0
  2.75     1026.0
  2.92      988.0
  3.08      950.0
  3.25      914.0
  3.42      880.0
  3.58      849.0
  3.75      819.0
  3.92      789.0
  4.08      760.0
  4.25      732.0
  4.42      703.0
  4.58      675.0
  4.75      652.0
  4.92      612.0
  5.08      586.0
  5.25      555.0
  0.083    8218.0
  0.167    7215.0
  0.33     5804.0
  0.5      5170.0
  0.67     4752.0
  0.83     4435.0
  1.0      4101.0
```

```
   1.167   3830.0
   1.33    3623.0
   1.5     3446.0
   1.67    3305.0
   1.83    3180.0
   2.0     3114.0
   2.167   3055.0
   2.33    2948.0
   2.5     2856.0
   2.67    2790.0
   2.83    2709.0
   3.0     2637.0
 END


 PROCED GargasFMParam
   SET VFatC=0.10, VMaxC=23.2
 END

 PROCED GargasFM
 ! Data from Abbas and Fisher (1997)
 ! Data from female_rat_mice_fisher.dat
 ! TCE - female B6C3F1 mice
 ! Female Mice Closed Chamber
   Mouse
   ResetDoses
   GargasFMParam
   SET BW=0.024, QPC=30.0
   SET Conc=300.0, CC=.TRUE.,
 NRats=14.0, kLossC=0.02, VChC=9.1
   SET TChng=7.0, Days=1.0, TMax=24.0,
 TStp=7.0
   START /NC
   SET NRWITG=.T.
   SET BW=0.021, Conc=700.0
   START /NC
   SET BW=0.022, Conc=1100.0
   START /NC
   SET BW=0.022, Conc=3700.0
   START /NC
   SET BW=0.022, Conc=7000.0
   START /NC
   PLOT CInhPPM/run=1, CInhPPM/run=2,
 CInhPPM/run=3, CInhPPM/run=4,
 CInhPPM/run=5, /DATA=gargasfm CInhPPM
 SET NRWITG=.F.
 END

 DATA GargasFM (T, CInhPPM)
   0.083    214.0
   0.5       99.0
   0.667     70.3
   0.83      52.3
   1.0       38.1
   1.167     28.5
   1.333     22.2
   1.500     16.9
   1.67      12.3
   1.83       9.4
   2.0        7.1
   0.083    624.0
   0.167    502.0
   0.333    357.0
   0.5      245.0
   0.667    179.0
   0.83     136.0
   1.0      108.0
   1.167     82.4
   1.333     63.7
   1.5       48.9
   1.67      40.5
   1.83      32.6
   2.0       27.4
   2.167     20.7
   2.333     16.2
   2.5       13.8
   2.67      11.7
   0.083    965.0
   0.167    803.0
   0.333    580.0
   0.5      467.0
   0.667    391.0
   0.83     314.0
   1.0      270.0
   1.167    235.0
   1.333    198.0
   1.5      160.0
   1.667    140.0
   1.83     119.0
   2.0      101.0
   2.167     86.2
   2.333     70.3
   2.5       59.1
   2.667     50.8
   2.83      41.8
   3.0       34.6
   3.167     28.7
   3.333     22.6
   3.5       19.4
   3.667     16.1
   3.83      13.5
   0.083   3611.0
   0.167   2854.0
   0.333   2269.0
   0.5     1848.0
   0.667   1569.0
   0.83    1276.0
   1.0     1244.0
   1.167   1147.0
   1.333   1080.0
   1.5      982.0
   1.667    940.0
   1.83     935.0
   2.0      897.0
   2.167    869.0
   2.333    840.0
   2.5      816.0
   2.667    792.0
   3.0      742.0
   3.167    719.0
   3.333    699.0
   3.5      676.0
   3.667    656.0
   3.83     621.0
   4.0      602.0
   4.167    578.0
```

```
  4.333    553.0
  4.5      530.0
  4.667    505.0
  4.83     480.0
  5.0      451.0
  5.167    429.0
  5.333    402.0
  5.5      374.0
  5.667    350.0
  6.0      297.0
  0.083   6401.0
  0.167   5475.0
  0.333   4161.0
  0.5     3303.0
  0.667   2868.0
  0.83    2702.0
  1.0     2467.0
  1.167   2290.0
  1.333   2203.0
  1.5     2122.0
  1.667   2048.0
  1.83    2004.0
  2.0     1984.0
  2.167   1951.0
  2.333   1913.0
  2.5     1885.0
  2.667   1801.0
  2.83    1776.0
  3.0     1771.0
  3.167   1753.0
  3.333   1736.0
  3.5     1711.0
  3.667   1689.0
  3.83    1667.0
  4.0     1647.0
  4.167   1622.0
  4.333   1599.0
  4.5     1574.0
  5.0     1556.0
  5.167   1531.0
  5.333   1446.0
  5.5     1418.0
  5.667   1389.0
  5.83    1369.0
  6.0     1320.0
END


PROCED Greenberg   ! TCE in blood
! Data from Greenberg MS, Burton GA,
and Fisher JW.  1999.
!  Physiologically based
pharmacokinetic modeling of inhaled
!  trichloroethylene and its oxidative
metabolites in B6C3F mice.
!  Toxicology and Applied Pharmacology
154:264-278.
!
! Male B6C3F1 mice (0.028-0.032 kg)
were exposed by inhalation to
!  100 or 600 ppm for up to 4 hours
! Greenberg et al. 1999. Mice -
Inhalation
!
! From procedure Greenberg in
TCENew.cmd
  Mouse
  ResetDoses
  SET ZZXERR=39*1.0e-9, ZZMERR=39*1.0e-
9
  SET Conc=100.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=48.0,
TStp=48.0
  START /NC

  SET NRWITG=.T., Conc=600.0
  SET ZZXERR=39*1.0e-8, ZZMERR=39*1.0e-
8
  START /NC
  PLOT CVen/run=1, CVen/run=2,
/DATA=greenberg1 CVen
  PLOT CTCOH/run=1, CTCOH/run=2,
/DATA=greenberg2 CTCOH
  PLOT CBldTCA/run=1, CBldTCA/run=2,
/DATA=greenberg3 CBldTCA
SET NRWITG=.F.
END


DATA Greenberg1 (T, CVen)
   2.0    0.672
   4.0    0.879
   4.25   0.139
   4.5    0.151
   2.0    6.791
   4.0    7.238
   4.25   1.507
   4.5    0.594
   4.75   0.461
   6.0    0.169
END

DATA Greenberg2 (T, CTCOH)
   2.0     1.948
   4.0     1.793
   4.25    1.749
   4.5     0.795
   4.75    0.301
   6.0     0.090
   2.0    15.386
   4.0    12.114
   4.25    9.880
   4.5     3.610
   4.75    2.944
   6.0     0.952
END

DATA Greenberg3 (T, CBldTCA)
   2.0     17.771
   4.25    29.296
   4.5     25.167
   4.75    30.500
   6.0     26.292
  12.0      6.945
  18.0      3.922
  28.0      1.965
```

```
    2.0     55.636
    4.25    71.795
    4.5     94.831
    4.75    93.010
    6.0    103.233
   12.0     24.451
   18.0     13.390
   28.0      7.196
   48.0      0.790
END

PROCED ProutMParam
  SET VMaxC=50.0, VMaxTCOHC=2.0,
kAD=0.3
END

PROCED ProutM
! Data from Prout et al. (1985)
! From procedures P3M, P5M, and P6M in
TCENew.cmd
! Mouse - 1000 mg/kg tce in oil
  Mouse
  ResetDoses
  SET ZZXERR=39*1.0e-7, ZZMERR=39*1.0e-
7
  ProutMParam
  SET BW=0.028, PDose=1000.0, Days=1.0,
TMax=1.0, TStp=45.0
  START /NC
  PLOT /DATA=proutm1 CVen
  PLOT /DATA=proutm2 CTCOH
  PLOT /DATA=proutm3 CBldTCA
END


DATA ProutM1 (T, CVen)
   0.09     9.81
   0.415   17.719
   0.753   13.021
   1.028    7.965
   1.638   10.105
   2.035    6.004
   2.717    5.831
   3.097    1.154
   3.571    1.329
   4.161    1.679
   4.714    2.17
   5.302    2.485
   5.766    2.554
   6.285    3.529
   6.766    3.864
   7.233    1.735
END

DATA ProutM2 (T, CTCOH)
   0.296    9.477
   0.588   21.574
   0.776   29.357
   1.012   27.676
   1.507   30.546
   2.08    27.443
   2.677   20.031
   3.487    9.369
   4.071   10.662
   4.578   14.157
   5.136    2.601
   5.443    7.302
   5.925    6.516
   6.641    5.316
   7.067    2.516
   7.563    1.166
   8.025    0.51
END

DATA ProutM3 (T, CBldTCA)
   0.804    38.161
   1.381   108.001
   1.778    68.642
   2.936   146.642
   3.552   122.081
   4.49    157.897
   5.009   134.087
   5.536   150.322
   5.864   101.92
   7.315   120.738
   7.822   162.399
   8.048   197.051
   8.707   209.215
   9.52    201.666
  10.12    189.58
  11.122   188.781
  12.916   170.32
  14.151   259.614
  15.243   240.369
  15.993   216.341
  16.121   179.322
  17.06    116.241
  18.557    59.745
  19.617   123.052
  20.712   196.42
  21.953   169.549
  22.4     145.33
  24.632   237.856
  25.757   223.972
  27.457   157.147
  28.877   150.795
  30.272   266.082
  31.375   283.333
  32.672    70.593
  33.491    56.951
  34.341    29.533
  35.625    28.261
  36.534    38.283
  38.911    28.988
  41.193    19.915
  44.214     7.202
END


PROCED TemplinMParam
  SET VMaxC=60.0, VMaxTCOHC=0.5,
kAD=1.0
END

PROCED TemplinM
```

```
! Data from Templin et al. (1993)
! From procedures T1TCE, T1TCA, T1TCOH,
and T1DCA in TCENew.cmd
! Also from data block TCE500 in
MouseB.cmd
! Mouse - 499.32 mg/kg TCE in 2% tween
  Mouse
  ResetDoses
  SET ZZXERR=39*1.0e-7, ZZMERR=39*1.0e-
7
  TemplinMParam
  SET BW=0.02, PDose=500.0, Days=1.0,
TMax=1.0, TStp=36.0
  START /NC
  PLOT /DATA=templinm1 CVen
  PLOT /DATA=templinm2 CBldTCA
  PLOT /DATA=templinm3 CTCOH
  PLOT /DATA=templinm4 CDCA
END

DATA TemplinM1 (T, CVen)
   0.267   27.871
   0.489   24.25
   0.756   21.428
   0.976   11.727
   1.479    3.827
   1.964    1.709
END

DATA TemplinM2 (T, CBldTCA)
   0.236   10.865
   0.531   18.549
   0.756   24.867
   1.03    42.942
   1.501   46.140
   2.024   43.821
   2.999   57.877
   3.977   64.961
   5.996   40.28
   9.002   38.183
  12.023   31.739
  17.858   10.926
  23.894    9.015
  35.888    1.990
END

DATA TemplinM3 (T, CTCOH)
   0.255   17.84
   0.756   35.8
   0.996   40.0
   1.491   30.0
   1.977    8.36
   2.949    0.72
END

DATA TemplinM4 (T, CDCA)
   0.229   0.787932
   0.499   4.658448
   0.756   4.728237
   0.971   5.141037
   1.469   5.768106
   2.949   2.965452
   5.965   1.68732
   8.98    0.785094
END


PROCED MouseM
! Data from Abbas and Fisher (1997)
! From procedures Mouse300M, Mouse600M,
Mouse1200M, Mouse2000M
!   TCE300, TCE600, TCE1200 and TCE2000
in MouseB.cmd
! Data also in TCA_CTCV_CTCL.xls
! Mice data--April 1996, TCE oral
gavage dosing in mice
! 300, 600, 1200, or 2000 mg/kg corn
oil gavage
!  Male
!  Mouse
  ResetDoses
  SET PDose=300.0, Days=1.0, TMax=24.0,
TStp=150.0
  START /NC
  PLOT /DATA=mouse300m1 CVen
  PLOT /DATA=mouse300m2 CLiv
  PLOT /DATA=mouse300m3 CFat
  PLOT /DATA=mouse300m4 CLivTCA
  PLOT /DATA=mouse300m5 CBldTCA
  PLOT /DATA=mouse300m6 AUrnTCA

  SET NRWITG=.T., PDose=600.0
  SET ZZXERR=39*1.0e-10,
ZZMERR=39*1.0e-10
  START /NC
  PLOT /DATA=mouse600m1 CVen
  PLOT /DATA=mouse600m2 CLiv
  PLOT /DATA=mouse600m3 CFat
  PLOT /DATA=mouse600m4 CLivTCA
  PLOT /DATA=mouse600m5 CBldTCA
  PLOT /DATA=mouse600m6 AUrnTCA

  SET PDose=1200.0
  START /NC
  PLOT /DATA=mouse1200m1 CVen
  PLOT /DATA=mouse1200m2 CLiv
  PLOT /DATA=mouse1200m3 CFat
  PLOT /DATA=mouse1200m4 CLivTCA
  PLOT /DATA=mouse1200m5 CBldTCA
  PLOT /DATA=mouse1200m6 AUrnTCA

  SET PDose=2000.0, TStp=200.0
  SET ZZXERR=39*1.0e-8, ZZMERR=39*1.0e-
8
  START /NC
  PLOT /DATA=mouse2000m1 CVen
  PLOT /DATA=mouse2000m2 CLiv
  PLOT /DATA=mouse2000m3 CFat
  PLOT /DATA=mouse2000m4 CLivTCA
  PLOT /DATA=mouse2000m5 CBldTCA
  PLOT /DATA=mouse2000m6 AUrnTCA
END

DATA Mouse300M1 (T, CVen)
   0.25   26.11
   0.5    12.99
```

```
   1.0      6.67
   2.0      0.68
   4.0      0.61
END

DATA Mouse300M2 (T, CLiv)
   0.25    70.0
   0.5     42.1
   1.0     16.98
   2.0      8.08
   4.0      4.17
   8.0      1.89
  16.0      0.945
  24.0      4.18
  30.0      3.39
  48.0      1.33
END

DATA Mouse300M3 (T, CFat)
   0.25     60.13
   0.5     125.4
   1.0     189.9
   2.0      72.58
   4.0      40.32
   8.0      18.12
  16.0      31.3
  24.0       0.65
  30.0       0.778
  48.0       0.32
END

DATA Mouse300M4 (T, CLivTCA)
    0.25    18.9
    2.0     35.8
    4.0     45.6
    8.0     48.0
   16.0     35.3
   24.0      8.16
   30.0     10.4
END

DATA Mouse300M5 (T, CBldTCA)
    0.25    26.7
    0.5     20.4
    2.0     42.6
    4.0     53.4
    8.0     47.6
   16.0     43.2
   24.0     35.9
   30.0     25.0
END

DATA Mouse300M6 (T, AUrnTCA)
   24.0    0.707
   48.0    1.176
   72.0    1.292
   96.0    1.304
  120.0    1.307
  144.0    1.308
END

DATA Mouse600M1 (T, CVen)
   0.25    81.9
   0.5     71.3
   2.0      5.71
   4.0      1.94
   8.0      0.965
  24.0      1.72
  30.0      0.72
  40.0      0.71
END

DATA Mouse600M2 (T, CLiv)
   0.25    213.5
   0.5     163.8
   2.0      19.43
   4.0      10.63
   8.0       0.71
  24.0       0.34
  30.0       0.26
  40.0       0.30
END

DATA Mouse600M3 (T, CFat)
   0.25    278.50
   0.5     659.0
   2.0     468.91
   4.0      46.76
   8.0       9.48
  24.0       0.13
  30.0       0.15
  40.0       0.12
END

DATA Mouse600M4 (T, CLivTCA)
    0.25    11.2
    0.5     22.9
    2.0     33.5
    4.0     39.9
    8.0     54.99
   16.0     39.06
   24.0     28.2
   30.0     15.3
   40.0      7.6
END

DATA Mouse600M5 (T, CBldTCA)
    0.25    11.18
    0.5     14.26
    2.0     26.98
    4.0     31.73
    8.0     31.87
   16.0     29.48
   24.0     24.81
   40.0     21.1
END

DATA Mouse600M6 (T, AUrnTCA)
   24.0    0.762
   48.0    1.683
   72.0    1.867
   96.0    1.904
  120.0    1.927
  144.0    1.941
END
```

```
DATA Mouse1200M1 (T, CVen)
   0.083    165.87
   0.17     191.31
   0.25     123.52
   0.5       86.9
   0.75      70.9
   1.0       43.08
   1.5       35.17
   2.0       20.36
   3.0        8.97
   4.0        7.50
   8.0        1.64
  12.0        0.72
  16.0        0.47
  24.0        0.52
  30.0        0.43
  40.0        0.45
END

DATA Mouse1200M2 (T, CLiv)
   0.083    522.6
   0.17     585.3
   0.25     499.4
   0.5      408.0
   0.75     289.8
   1.0      228.8
   1.5       63.04
   2.0       38.97
   3.0       59.74
   4.0       26.5
   6.0       15.37
   8.0       14.97
  16.0       12.86
  24.0        1.79
  30.0        1.27
  40.0        1.42
END

DATA Mouse1200M4 (T, CFat)
   0.083       61.53
   0.17       156.7
   0.25       567.2
   0.5        826.0
   0.75       865.3
   1.5       1199.9
   2.0       1050.5
   3.0        550.2
   4.0        485.0
   6.0        219.2
   8.0        293.7
  16.0          4.400
  24.0          1.446
  30.0          1.121
  40.0          1.507
END

DATA Mouse1200M4 (T, CLivTCA)
     0.083     5.69
     0.17      6.2
     0.25     11.09
     0.5      16.95
     0.75     20.09
     1.0      26.02
     1.5      29.44
     2.0      35.65
     3.0      37.76
     4.0      42.07
     6.0      43.92
     8.0      57.83
    16.0      27.71
    24.0      22.67
    40.0       6.34
END

DATA Mouse1200M5(T, CBldTCA)
     0.083     5.01
     0.17     11.2
     0.25     16.5
     0.5      23.1
     0.75     29.2
     1.0      36.1
     1.5      41.8
     2.0      59.1
     3.0      64.0
     4.0      70.2
     6.0      94.1
     8.0      90.8
    16.0      65.2
    24.0      43.86
    30.0      41.48
    40.0       9.15
END

DATA Mouse1200M6(T, AUrnTCA)
    24.0    2.294
    48.0    3.731
    72.0    4.579
    96.0    4.796
   120.0    4.848
   144.0    4.878
END

DATA Mouse2000M1  (T, CVen)
    0.25    208.3
    0.5     162.01
    1.0     140.1
    2.0      64.8
    4.0      48.6
    8.0      17.48
   16.0       9.4
   24.0       1.15
   40.0       0.78
END

DATA Mouse2000M2  (T, CLiv)
    0.25   1498.0
    0.5     335.0
    1.0     379.7
    2.0     116.2
   16.0       9.2
   24.0       2.0
   30.0       1.2
   40.0       0.3
END

DATA Mouse2000M3  (T, CFat)
```

```
    0.25   1152.0
    0.5    1993.0
    1.0    4279.0
    2.0    2015.0
    4.0    1991.0
    8.0    1503.0
   16.0      75.5
   24.0       7.4
 END

 DATA Mouse2000M4 (T, CLivTCA)
     0.25    15.18
     0.5     27.58
     1.0     37.49
     2.0     49.46
     4.0     65.32
     8.0    105.65
    16.0    59.0
    24.0    44.6
    30.0    36.35
    48.0     9.98
 END

 DATA Mouse2000M5 (T, CBldTCA)
     0.25    11.22
     0.5     20.57
     1.0     30.34
     2.0     43.51
     4.0     63.43
    16.0    131.85
    24.0     51.38
    30.0     54.57
    48.0      8.74
 END

 DATA Mouse2000M6 (T, AUrnTCA)
    24.0   1.423
    48.0   2.486
    72.0   3.122
    96.0   3.294
   120.0   3.395
   144.0   3.426
   168.0   3.438
   192.0   3.450
 END


 PROCED BernRParam
   SET KM=12.0
 END

 PROCED BernR
 ! Data from Bernauer et al. (1996) --
 Rats
 ! From procedure BernR in TCENew.cmd
 ! Rats -- 40, 80, 160 ppm TCE for 6
 hours
   Rat
   ResetDoses
   BernRParam
   SET BW=0.275
   SET Conc=40.0, CC=.FALSE., TChng=6.0,
 Days=1.0, TMax=6.0, TStp=50.0
   START /NC
   D AUrnTCTotMole, AUrnNDCVCMole,
 AUrnNDCVC

   SET NRWITG=.T., Conc=80.0
   START /NC
   D AUrnTCTotMole, AUrnNDCVCMole,
 AUrnNDCVC

   SET Conc=160.0
   START /NC
   D AUrnTCTotMole, AUrnNDCVCMole,
 AUrnNDCVC

   PLOT AUrnTCTotMole/run=1,
 AUrnTCTotMole/run=2,
 AUrnTCTotMole/run=3, /DATA=bernr1
 AUrnTCTotMole
   PLOT AUrnNDCVCMole/run=1,
 AUrnNDCVCMole/run=2,
 AUrnNDCVCMole/run=3, /DATA=bernr2
 AUrnNDCVCMole

   PLOT AUrnTCA/run=1, AUrnTCA/run=2,
 AUrnTCA/run=3, /DATA=bernr3 AUrnTCA
   PLOT AUrnTCOGTCOH/run=1,
 AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
 /DATA=bernr4 AUrnTCOGTCOH
   PLOT AUrnNDCVC/run=1,
 AUrnNDCVC/run=2, AUrnNDCVC/run=3,
 /DATA=bernr5 AUrnNDCVC
 SET NRWITG=.F.
 END

 DATA BernR1 (T, AUrnTCTotMole)
   48.0   0.0069
   48.0   0.0130
   48.0   0.0333
 END

 DATA BernR2 (T, AUrnNDCVCMole)
   48.0   0.000007
   48.0   0.000010
   48.0   0.000013
 END

 DATA BernR3 (T, AUrnTCA)
   12.0   0.061
   24.0   0.061
   36.0   0.061
   48.0   0.061
   12.0   0.131
   24.0   0.210
   36.0   0.256
   48.0   0.281
   12.0   0.563
   24.0   0.858
   36.0   0.995
   48.0   1.063
 END

 DATA BernR4 (T, AUrnTCOGTCOH)
   12.0   1.166
```

```
  24.0   1.234
  36.0   1.309
  48.0   1.345
  12.0   2.338
  24.0   2.827
  36.0   3.100
  48.0   3.294
  12.0   3.850
  24.0   4.320
  36.0   4.666
  48.0   4.937
END

DATA BernR5 (T, AUrnNDCVC)
  12.0   5.41e-5
  24.0   1.42e-4
  36.0   1.95e-4
  48.0   2.71e-4
  12.0   1.23e-4
  24.0   2.63e-4
  36.0   4.05e-4
  48.0   5.71e-4
  12.0   2.13e-4
  24.0   6.72e-4
  36.0   1.24e-3
  48.0   1.59e-3
END


PROCED FisherMR
! Data from Fisher et al. (1991)
! From procedures FG2B and FG2D in
TCENew.cmd
! 505 ppm TCE 4 hr -- Male Rat
  Rat
  ResetDoses
  SET Conc=505.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=33.0
  START /NC
  PLOT /DATA=fishermr1 CBldTCA

  SET Conc=529.0, TStp=11.0
  START /NC
  PLOT /DATA=fishermr2 CVen
END

DATA FisherMR1 (T, CBldTCA)
   1.97     6.445
   3.915   11.179
   5.986   22.381
   7.982   21.866
  10.099   20.455
  12.099   17.526
  26.216    6.232
  32.139    4.561
END

DATA FisherMR2 (T, CVen)
   1.976   21.091
   3.981   34.209
   6.031    6.027
   8.031    1.662
  10.054    0.986
END


PROCED FisherFRParam
  SET QPC=15.0, VMaxC=20.0
END

PROCED FisherFR
! Data from Fisher et al. (1991)
! From procedures FG2A and FG2C in
TCENew.cmd
! 600 ppm TCE 4 hr -- Female Rat
  Rat
  ResetDoses
  FisherFRParam
  SET Conc=600.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=50.0
  START /NC
  PLOT /DATA=fisherfr1 CVen
  PLOT /DATA=fisherfr2 CBldTCA
END

DATA FisherFR1 (T, CVen)
   0.498    9.448
   3.556   25.889
   4.215   19.272
   5.033    6.865
   6.009    3.341
END

DATA FisherFR2 (T, CBldTCA)
   0.622    2.137
   3.677   20.408
   4.44    19.485
   5.196   31.914
   6.175   33.11
   8.661   39.233
  25.972   11.036
  32.033    6.03
  49.023    1.362
END


PROCED GargasR
! Data from Andersen et al. (1987)
! Data from CC.dat from Mike Gargas
! Rat Closed Chamber
  Rat
  ResetDoses
  SET BW=0.256
  SET Conc=100.0, CC=.TRUE., NRats=3.0,
kLossC=0.01, VChC=9.1
  SET TChng=6.0, Days=1.0, TMax=24.0,
TStp=6.0
  START /NC
  SET NRWITG=.T.
  SET BW=0.249, Conc=450.0
  START /NC
  SET BW=0.274, Conc=1000.0
  START /NC
  SET BW=0.269, Conc=2000.0
```

```
  START /NC
  SET BW=0.272, Conc=4640.0
  START /NC
  PLOT CInhPPM/run=1, CInhPPM/run=2,
CInhPPM/run=3, CInhPPM/run=4,
CInhPPM/run=5, /DATA=gargasr CInhPPM
SET NRWITG=.F.
END

DATA GargasR (T, CInhPPM)
  0.083      92.30
  0.167      76.10
  0.333      54.90
  0.500      41.00
  0.667      31.30
  0.833      21.70
  1.000      16.30
  1.167      13.00
  1.333      10.00
  1.500       7.90
  1.667       6.30
  1.833       5.40
  2.000       4.80
  2.167       4.30
  2.333       3.20
  0.083     435.00
  0.167     375.00
  0.333     270.00
  0.500     206.00
  0.667     153.00
  0.833     116.00
  1.000      89.20
  1.167      69.10
  1.333      50.30
  1.500      37.40
  1.667      28.50
  1.833      22.00
  2.000      18.20
  2.167      15.00
  2.333      11.20
  2.500       9.52
  2.667       7.82
  0.083     884.00
  0.167     738.00
  0.333     519.00
  0.500     406.00
  0.667     312.00
  0.833     259.00
  1.000     215.00
  1.167     184.00
  1.333     152.00
  1.500     128.00
  1.667     111.00
  1.833      94.00
  2.000      82.00
  2.167      70.00
  2.333      58.00
  2.500      50.00
  2.667      45.00
  2.833      38.00
  3.000      32.00
  3.167      26.00
  3.333      23.00
  3.500      19.00
  3.667      17.00
  3.833      15.00
  4.000      14.00
  4.167      13.00
  4.333      11.00
  0.083    1741.00
  0.167    1460.00
  0.333    1076.00
  0.500     887.00
  0.667     697.00
  0.833     580.00
  1.000     501.00
  1.167     427.00
  1.333     369.00
  1.500     324.00
  1.667     276.00
  1.833     259.00
  2.000     240.00
  2.167     236.00
  2.333     218.00
  2.500     198.00
  2.667     195.00
  2.833     181.00
  3.000     165.00
  3.167     162.00
  3.333     152.00
  3.500     145.00
  3.667     138.00
  3.833     132.00
  4.000     122.00
  4.167     113.00
  4.333     104.00
  4.500      95.10
  4.667      88.10
  4.833      82.30
  5.000      74.10
  5.167      62.10
  5.333      61.90
  5.500      55.40
  5.667      52.90
  5.833      48.30
  6.000      45.00
  0.083    3986.00
  0.167    3333.00
  0.333    2443.00
  0.500    1904.00
  0.667    1553.00
  0.833    1298.00
  1.000    1128.00
  1.167    1004.00
  1.333     902.00
  1.500     825.00
  1.667     775.00
  1.833     724.00
  2.000     675.00
  2.167     661.00
  2.333     631.00
  2.500     612.00
  2.667     591.00
  2.833     570.00
  3.000     556.00
  3.167     538.00
```

```
   3.333    535.00
   3.500    522.00
   3.667    512.00
   3.833    500.00
   4.000    498.00
   4.167    486.00
   4.333    474.00
   4.500    472.00
   4.667    465.00
   4.833    455.00
   5.000    445.00
   5.167    439.00
   5.333    436.00
   5.583    428.00
   5.667    418.00
   5.833    409.00
   6.000    403.00
END


PROCED LarsonRParam
  SET FracTCE=0.02, VMaxGlucC=20.0
END

PROCED LarsonR
! Data from Larson and Bull (1992)
! From procedures LarTCE1-LarTCE3,
LarTCA1-LarTCA3, and LarTOH1-LarTOH3
!  in TCENew.cmd
! Rat - 200 mg/kg TCE in 1% tween
  Rat
  ResetDoses
  LarsonRParam
  SET PDose=200.0, Days=1.0, TMax=24.0,
TStp=48.0
  START /NC
  PLOT /DATA=larsonr1a CVen
  PLOT /DATA=larsonr1b CBldTCA
  PLOT /DATA=larsonr1c CTCOH

! Rat - 600 mg/kg TCE in 1% tween
  SET PDose=600.0
  START /NC
  PLOT /DATA=larsonr2a CVen
  PLOT /DATA=larsonr2b CBldTCA
  PLOT /DATA=larsonr2c CTCOH

! Rat - 2996 mg/kg TCE in 1% tween
  SET PDose=2996.0, TStp=73.0
  SET ZZXERR=39*1.0e-7, ZZMERR=39*1.0e-
7
  START /NC
  PLOT /DATA=larsonr3a CVen
  PLOT /DATA=larsonr3b CBldTCA
  PLOT /DATA=larsonr3c CTCOH
END

DATA LarsonR1a (T, CVen)
   1.0    9.745938
   2.0    5.031306
   4.0    2.116854
   8.0    1.069596
  12.0    0.36135
END

DATA LarsonR1b (T, CBldTCA)
   1.0     5.36769
   2.0     7.650388
   4.0    11.841598
   8.0    12.996836
  12.0    10.447796
  24.0     1.516352
  48.0     0.047386
END

DATA LarsonR1c (T, CTCOH)
   1.0    13.27261
   2.0    22.883965
   4.0    23.739105
   8.0     6.07269
  12.0     2.17373
  24.0     0.399165
END

DATA LarsonR2a (T, CVen)
   1.0    26.530974
   2.0    34.693542
   4.0    20.953044
   8.0    6.132438
  12.0    2.934162
  24.0    0.674082
END

DATA LarsonR2b (T, CBldTCA)
   1.0     2.828454
   2.0     6.370966
   4.0     9.233734
   8.0    20.766506
  12.0    24.740394
  24.0    17.43478
  48.0     0.042484
END

DATA LarsonR2c (T, CTCOH)
   1.0    13.47294
   2.0    16.94134
   4.0    27.195545
   8.0    44.252
  12.0    32.46542
  24.0     4.75111
  48.0     0.145015
END

DATA LarsonR3a (T, CVen)
   1.0     69.226776
   2.0    185.690538
   4.0    120.072006
   8.0     98.804916
  12.0     55.408752
  24.0      7.852464
  48.0      0.237834
END

DATA LarsonR3b (T, CBldTCA)
   1.0     4.058856
   2.0    10.104656
```

```
   4.0   11.207606
   8.0   23.965878
  12.0   28.884218
  24.0   61.918796
  48.0    5.496776
  72.0    0.165034
END

DATA LarsonR3c (T, CTCOH)
   1.0   17.48851
   2.0   29.883555
   4.0   29.961295
   8.0   33.76906
  12.0   51.827165
  24.0   34.89928
  48.0    0.86411
END


PROCED ProutR
! Data from Prout et al. (1985)
! From procedures P3R, P5R, and P6R in
TCENew.cmd
! Rat - 1000 mg/kg TCE in corn oil
  Rat
  ResetDoses
  SET BW=0.19, PDose=1000.0, Days=1.0,
TMax=1.0, TStp=40.0
  START /NC
  PLOT /DATA=proutr1 CVen
  PLOT /DATA=proutr2 CTCOH
  PLOT /DATA=proutr3 CBldTCA
END

DATA ProutR1 (T, CVen)
   0.058    5.227
   0.201   14.055
   0.431   19.529
   0.616   24.837
   1.358   19.794
   1.742   23.578
   2.301   42.371
   3.015   62.47
   4.06    43.553
   4.507   40.977
   5.121   29.243
   5.707   28.869
   6.148   28.964
   7.105   21.193
   8.092   18.967
   9.33    13.418
  10.354   11.543
  11.279    8.631
END

DATA ProutR2 (T, CTCOH)
   1.042   0.802
   1.531   0.989
   2.105   0.889
   2.597   0.778
   3.091   0.773
   3.48    0.767
   4.06    1.092
   4.513   1.256
   5.182   0.774
   5.55    1.126
   6.068   0.933
   6.663   1.229
   7.149   0.655
   8.118   0.918
   9.113   1.455
  10.001   7.222
  11.14    2.062
  12.033   2.214
  13.026   1.278
  13.955   0.592
  14.975   1.994
  16.041   0.772
  17.016   0.92
  18.071   0.71
END

DATA ProutR3 (T, CBldTCA)
   2.153    3.391
   3.815    4.492
   4.723   10.821
   6.058   10.155
   6.918   14.629
   8.071   14.598
   9.365   25.456
  10.354   18.378
  11.496   45.88
  12.31    38.522
  13.248   49.159
  15.695   28.235
  17.43    34.252
  19.366   44.523
  20.272   40.253
  21.761   24.383
  22.843   18.858
  24.838   14.865
  25.888   14.386
  28.323   22.531
  29.447   32.197
  30.457   38.11
  31.603   32.229
  33.151   19.265
  34.613   20.718
  36.365   20.975
  39.99     6.918
END


PROCED TemplinRParam
  SET FracTCE=0.01, VMaxTCOHC=0.06,
VMaxGlucC=150.0, kEHRC=0.3, kAD=0.6
END

PROCED TemplinR
! Data from Templin et al. (1995)
! From procedures TT, TC, and TS in
TCENew.cmd
! Rat - 100 mg/kg TCE in 2% tween
  Rat
  ResetDoses
```

```
  TemplinRParam
  SET BW=0.2, PDose=100.0, Days=1.0,
TMax=24.0, TStp=48.0
  START /NC
  PLOT /DATA=templinr1 CVen
  PLOT /DATA=templinr2 CBldTCA
  PLOT /DATA=templinr3 CTCOH
END

DATA TemplinR1 (T, CVen)
   0.252    5.627367
   0.494    8.889005
   0.736   10.184595
   0.993    6.760255
   1.49     2.313853
   1.972    1.55759
   2.475    0.922502
END

DATA TemplinR2 (T, CBldTCA)
   0.252   0.951757
   0.494   1.410765
   0.728   1.923237
   0.984   1.645322
   1.958   4.274023
   2.475   3.862448
   2.984   4.968566
   3.987   6.032467
   4.97    6.719023
   5.97    6.954884
   8.979   7.540054
  11.98    7.226116
  23.963   4.362369
  47.986   1.516552
END

DATA TemplinR3 (T, CTCOH)
   0.233   0.8934
   0.482   1.5903
   0.728   1.97115
   0.961   2.0589
   1.463   2.0523
   1.962   2.7261
   2.455   3.28275
   2.958   2.7078
   3.972   2.52705
   5.017   2.24115
   5.984   2.06565
   8.964   1.02
END


PROCED BernH
! Data from Bernauer et al. (1996) --
Human
! From procedure BernH in TCENew.cmd
! Human -- 40, 80, 160 ppm TCE for 6
hours
  Human
  ResetDoses
  SET Conc=40.0, CC=.FALSE., TChng=6.0,
Days=1.0, TMax=6.0, TStp=54.0
  START /NC
  D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

  SET NRWITG=.T., Conc=80.0
  START /NC
  D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

  SET Conc=160.0
  START /NC
  D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

  PLOT AUrnTCTotMole/run=1,
AUrnTCTotMole/run=2,
AUrnTCTotMole/run=3, /DATA=bernh1
AUrnTCTotMole
  PLOT AUrnNDCVCMole/run=1,
AUrnNDCVCMole/run=2,
AUrnNDCVCMole/run=3, /DATA=bernh2
AUrnNDCVCMole

  PLOT AUrnTCA/run=1, AUrnTCA/run=2,
AUrnTCA/run=3, /DATA=bernh3 AUrnTCA
  PLOT AUrnTCOGTCOH/run=1,
AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
/DATA=bernh4 AUrnTCOGTCOH
  PLOT AUrnNDCVC/run=1,
AUrnNDCVC/run=2, AUrnNDCVC/run=3,
/DATA=bernh5 AUrnNDCVC
SET NRWITG=.F.
END

DATA BernH1 (T, AUrnTCTotMole)
  54.0   0.823
  54.0   1.775
  54.0   3.080
END

DATA BernH2 (T, AUrnNDCVCMole)
  54.0   0.00025
  54.0   0.00037
  54.0   0.00043
END

DATA BernH3 (T, AUrnTCA)
   6.0    0.84
  11.0    1.56
  16.0    3.37
  23.0    6.19
  30.0    9.73
  35.0   11.49
  40.0   13.20
  47.0   15.14
  54.0   16.46
   6.0    2.06
  11.0    4.27
  16.0    6.52
  23.0   10.49
  30.0   17.08
  35.0   21.57
  40.0   26.87
  47.0   31.84
```

```
  54.0   37.96
   6.0    2.29
  11.0    5.71
  16.0   10.74
  23.0   18.57
  30.0   28.08
  35.0   34.58
  40.0   41.75
  47.0   49.31
  54.0   57.51
END

DATA BernH4 (T, AUrnTCOGTCOH)
   6.0    12.65
  11.0    28.58
  16.0    43.41
  23.0    53.72
  30.0    65.12
  35.0    73.70
  40.0    81.61
  47.0    88.40
  54.0    93.21
   6.0    37.44
  11.0    79.43
  16.0   112.69
  23.0   145.30
  30.0   173.21
  35.0   188.35
  40.0   201.73
  47.0   217.09
  54.0   230.08
   6.0    52.50
  11.0   113.78
  16.0   168.73
  23.0   222.17
  30.0   243.14
  35.0   263.43
  40.0   280.17
  47.0   294.98
  54.0   311.45
END

DATA BernH5 (T, AUrnNDCVC)
   6.0   0.0015
  11.0   0.0028
  16.0   0.0049
  23.0   0.0068
  30.0   0.0124
  35.0   0.0144
  40.0   0.0163
  47.0   0.0180
  54.0   0.0193
   6.0   0.0035
  11.0   0.0055
  16.0   0.0113
  23.0   0.0152
  30.0   0.0262
  35.0   0.0306
  40.0   0.0347
  47.0   0.0384
  54.0   0.0416
   6.0   0.0051
  11.0   0.0118
  16.0   0.0225
  23.0   0.0301
  30.0   0.0368
  35.0   0.0382
  40.0   0.0447
  47.0   0.0531
  54.0   0.0577
END

PROCED MonsterParam
  SET VBodC=0.12, VMaxc=18.0,
VMaxTCOHC=12.0, kUrnTCAC=0.15
END

PROCED Monster
! Data from Monster et al. (1979)
! From procedures AF3A-AF3F and AF5A-
AF5D in TCENew.cmd
! 70 ppm TCE -- Human
  Human
  ResetDoses
  MonsterParam
  SET Conc=70.0, CC=.FALSE., TChng=4.0,
Days=5.0, TMax=150.0, TStp=340.0
  START /NC
  PLOT /DATA=monster1 CVen
  PLOT /DATA=monster2 CBldTCA
  PLOT /DATA=monster3 AUrnTCA
  PLOT /DATA=monster4 CAlvPPM
  PLOT /DATA=monster5 TotCTCOH
  PLOT /DATA=monster6 AUrnTCOGTCOH
END

DATA Monster1 (T, CVen)
    4.0     2.2
    5.4     0.33
   22.0     0.014
   28.0     2.2
   29.4     0.3
   46.0     0.02
   52.0     2.2
   53.4     0.33
   70.0     0.027
   76.0     2.2
   77.4     0.365
   94.0     0.027
  100.0     2.209
  101.4     0.361
  118.0     0.03
END

DATA Monster2 (T, CBldTCA)
    2.807    4.484
    3.899    7.958
   22.0     13.177
   27.956   21.134
   45.658   24.953
   48.779   33.159
   52.451   33.057
   69.989   36.207
   75.3     38.465
   75.772   43.948
```

```
  94.43    48.398
  98.451   50.838
 100.291   51.825
 118.458   50.265
 165.324   38.583
 237.579   21.545
 334.247    9.462
END

DATA Monster3 (T, AUrnTCA)
    2.277      1.607
   10.14       5.542
   17.883      9.98
   26.19      16.14
   33.796     27.248
   41.501     35.067
   49.78      48.356
   57.61      65.827
   66.042     77.979
   74.02      96.759
   81.924    121.256
   90.081    141.155
   98.153    167.439
  106.014    198.695
  114.175    218.116
  122.134    246.406
  129.989    273.143
  138.0      289.619
  146.006    308.377
  153.675    328.452
  161.622    342.279
  169.804    348.791
  177.792    357.064
  185.706    362.083
END

DATA Monster4 (T, CAlvPPM)
   1.041    8.909
   1.959    8.914
   2.942   13.337
   3.969   14.060
   4.949   18.097
   5.968   13.956
   6.368    5.407
   7.007    2.765
   7.032    4.025
   8.016    2.589
   9.026    1.549
   9.991    0.770
  11.987    0.388
  13.978    0.393
  24.586    0.199
  35.520    0.103
  48.493    0.065
  59.576    0.061
   0.030    1.280
   1.009    6.968
   2.018    8.344
   2.970   10.207
   3.989   11.057
   4.966   13.605
   5.924   11.602
   6.077    6.861
   6.269    5.581
   6.434    3.635
   6.919    2.997
   7.426    2.488
   7.895    2.396
   8.892    1.532
   9.913    1.342
  13.902    0.681
  23.996    0.420
END


DATA Monster5 (T, TotCTCOH)
   0.984   0.775
   2.034   1.807
   3.006   2.638
   4.009   3.490
   5.044   4.332
   6.007   5.941
   6.216   4.647
   6.646   4.943
   7.010   5.030
   8.018   4.589
   9.008   3.715
   9.997   3.719
  12.005   3.129
  14.007   2.771
  24.546   1.265
  35.566   0.829
  49.399   0.336
  59.480   0.245
   0.025   0.024
   1.003   1.010
   3.025   2.419
   4.058   3.367
   5.082   3.675
   6.051   4.477
   6.396   4.525
   6.523   4.477
   6.798   4.444
   7.040   4.401
   7.597   4.031
   8.101   4.006
   9.099   3.623
  10.090   3.082
  14.034   2.399
  23.999   1.069
END

DATA Monster6 (T, AUrnTCOGTCOH)
     3.912     51.482
    11.904    106.747
    20.184    138.360
    27.984    202.971
    36.072    284.271
    44.064    320.665
    52.128    393.523
    60.312    471.060
    68.232    512.698
    76.368    591.433
    84.552    671.339
    92.736    717.257
   100.704    795.718
```

```
   108.696    884.483
   116.472    928.646
   124.656    959.874
   132.672    976.041
   140.760    986.787
   148.344    998.355
   156.192   1006.748
   163.992   1012.067
   243.912   1014.424
   251.976   1016.263
   259.968   1017.808
 END


 PROCED Monster2
 ! Data from Monster et al. (1979)
 ! From procedure Monster in HumanB.cmd
 !  Male
   Human
   ResetDoses
   SET BW=69.7
   SET Conc=70.0, CC=.FALSE., TChng=4.0,
 Days=1.0, TMax=24.0, TStp=220.0
   START /NC
   PLOT /DATA=mon70a CBldTCA
   PLOT /DATA=mon70b AUrnTCOGTCOH
   PLOT /DATA=mon70c AUrnTCA
   PLOT /DATA=mon70d CTCOH

   SET Conc=140.0
   START /NC
   PLOT /DATA=mon140a CBldTCA
   PLOT /DATA=mon140b AUrnTCOGTCOH
   PLOT /DATA=mon140c AUrnTCA
   PLOT /DATA=mon140d CTCOH
 END

 DATA Mon70a (T, CBldTCA)
     4.0   3.5
     6.0   5.1
    24.0   8.19
    48.0   8.97
    72.0   8.58
   144.0   5.07
   216.0   2.73
 END

 DATA Mon70b (T, AUrnTCOGTCOH)
     6.0    35.3
    14.0    86.4
    22.0   113.4
    30.0   133.7
    38.0   143.5
    46.0   149.2
    54.0   153.4
    62.0   158.1
    70.0   160.7
 END

 DATA Mon70c (T, AUrnTCA)
    22.0    7.0
    46.0   18.7
    70.0   26.5
 END

 DATA Mon70d (T, CTCOH)
     4.0   4.4
     6.0   4.1
    24.0   0.91
 END

 DATA Mon140a (T, CBldTCA)
     4.0    3.8
     6.0    6.0
    24.0   11.3
    48.0   12.8
    72.0   11.3
   144.0    7.55
   216.0    4.5
 END

 DATA Mon140b (T, AUrnTCOGTCOH)
     6.0    55.1
    14.0   153.9
    22.0   206.8
    30.0   243.3
    38.0   265.3
    46.0   276.4
    54.0   284.0
    62.0   290.0
 END

 DATA Mon140c (T, AUrnTCA)
    22.0    7.6
    46.0   24.1
    70.0   42.3
 END

 DATA Mon140d (T, CTCOH)
     4.0   6.4
     6.0   7.2
    24.0   2.5
    48.0   0.6
 END


 PROCED MullerSingleParam
   SET VBodC=0.12, kUrnTCAC=0.15
 END

 PROCED MullerSingle
 ! Data from Muller et al. (1974, 1975)
 ! From procedures AF7A-AF7D in
 TCENew.cmd
 ! 100 ppm TCE -- Human
   Human
   ResetDoses
   MullerSingleParam
   SET Conc=100.0, CC=.FALSE.,
 TChng=6.0, Days=1.0, TMax=24.0,
 TStp=75.0
   START /NC
   PLOT /DATA=mullersingle1 CVen
   PLOT /DATA=mullersingle2 CBldTCA
   PLOT /DATA=mullersingle3 AUrnTCA
   PLOT /DATA=mullersingle4 TotCTCOH
```

```
  PLOT /DATA=mullersingle5 AUrnTCOGTCOH
  PLOT /DATA=mullersingle6 CAlvPPM
END

DATA MullerSingle1 (T, CVen)
   0.965   0.67
   1.879   1.105
   2.9     0.961
   3.876   0.859
   4.8     0.994
   5.992   1.093
   6.396   0.756
   6.736   0.539
   7.851   0.323
   8.86    0.217
   9.915   0.179
  11.853   0.14
  13.741   0.11
  23.769   0.072
  35.864   0.034
  47.915   0.031
  59.823   0.023
   1.021   0.804
   2.954   1.014
   3.944   1.407
   4.921   1.1
   5.898   1.318
   6.195   0.93
   6.369   0.617
   6.749   0.732
   7.362   0.561
   7.887   0.441
   8.891   0.381
   9.897   0.289
  13.864   0.16
  23.731   0.073
END

DATA MullerSingle2 (T, CBldTCA)
   0.974    2.553
   2.032    8.048
   3.965   12.369
   5.913   19.65
   7.946   26.426
   9.915   31.304
  11.92    36.274
  13.897   39.523
  13.902   39.419
  23.873   47.577
  35.93    43.756
  48.006   40.306
  59.891   38.657
   1.996    4.038
   4.0      8.087
   6.011   13.162
   8.011   17.286
  10.006   19.154
  13.985   20.938
  23.887   28.444
END

DATA MullerSingle3 (T, AUrnTCA)
  23.826    41.585
  47.946    86.675
  72.156   122.458
   2.970     0.484
   6.457     3.771
   8.533     6.289
  10.468    10.26
  23.859    25.593
END

DATA MullerSingle4 (T, TotCTCOH)
   0.984   0.775
   2.032   1.807
   3.006   2.638
   4.009   3.490
   5.044   4.332
   6.007   5.941
   6.216   4.647
   6.646   4.943
   7.008   5.030
   8.017   4.589
   9.008   3.715
   9.994   3.719
  12.005   3.129
  14.007   2.771
  24.546   1.265
  35.566   0.829
  49.399   0.336
  59.480   0.245
   0.027   0.024
   1.006   1.010
   3.025   2.419
   4.058   3.367
   5.082   3.675
   6.051   4.477
   6.396   4.525
   6.523   4.477
   6.798   4.444
   7.040   4.401
   7.597   4.031
   8.101   4.006
   9.099   3.623
  10.090   3.082
  14.034   2.399
  23.997   1.069
END

DATA MullerSingle5 (T, AUrnTCOGTCOH)
  24.0     245.244
  48.0     301.207
  72.0     316.49
   3.158    18.6
   6.573    71.2
   8.634   107.2
  10.627   142.3
  24.47    233.1
END

DATA MullerSingle6 (T, CAlvPPM)
   1.041    8.909
   1.959    8.914
   2.942   13.337
   3.965   14.060
   4.949   18.097
```

```
   5.968   13.956
   6.368    5.407
   7.008    2.765
   7.032    4.025
   8.017    2.589
   9.026    1.549
   9.994    0.770
  11.987    0.388
  13.978    0.393
  24.586    0.199
  35.520    0.103
  48.493    0.065
  59.576    0.061
   0.027    1.280
   1.006    6.968
   2.018    8.344
   2.970   10.207
   3.989   11.057
   4.966   13.605
   5.924   11.602
   6.077    6.861
   6.269    5.581
   6.434    3.635
   6.919    2.997
   7.426    2.488
   7.895    2.396
   8.891    1.532
   9.913    1.342
  13.902    0.681
  23.997    0.420
END


PROCED MullerMultiParam
  SET VMaxC=8.0, VMaxTCOHC=30.0
END

PROCED MullerMulti
! Data from Muller et al. (1974, 1975)
! From procedures AF7A-AF7D in
TCENew.cmd
! 50 ppm TCE -- Human
  Human
  ResetDoses
  MullerMultiParam
  SET Conc=50.0, CC=.FALSE., TChng=6.0,
Days=5.0, TMax=150.0, TStp=430.0
  START /NC
  PLOT /DATA=mullermulti1 CBldTCA
  PLOT /DATA=mullermulti2 AUrnTCA
  PLOT /DATA=mullermulti3 TotCTCOH
  PLOT /DATA=mullermulti4 AUrnTCOGTCOH
END

DATA MullerMulti1 (T, CBldTCA)
    0.338    5.501
    7.905   13.882
    9.745   17.048
   23.744   17.932
   29.249   27.023
   32.948   29.95
   46.87    27.981
   52.887   36.986
   57.38    38.724
   71.086   35.964
   76.223   42.944
   80.282   43.978
   94.18    41.804
  100.307   49.053
  104.611   51.055
  118.7     49.005
  142.839   42.958
  201.431   29.181
  249.517   19.104
  287.758   15.022
  345.641   11.051
  419.058    5.815
END

DATA MullerMulti2 (T, AUrnTCA)
   22.913    19.094
   46.855    57.6
   69.715   124.243
   93.319   198.682
  117.8     297.932
  141.622   386.56
END

DATA MullerMulti3 (T, TotCTCOH)
   13.800   1.703
   18.312   1.318
   32.520   0.428
   38.616   2.079
   42.480   1.318
   56.088   0.606
   62.880   2.197
   67.176   1.513
   80.424   0.710
   86.736   2.257
   90.720   1.519
  104.184   0.649
  110.784   2.270
  115.080   1.640
  129.672   0.665
  155.304   0.202
  212.664   0.075
END

DATA MullerMulti4 (T, AUrnTCOGTCOH)
   24.0   102.573
   48.0   236.288
   72.0   380.370
   96.0   529.931
  120.0   687.668
  144.0   721.680
  192.0   725.865
  240.0   728.355
END


PROCED Muller72
! Data from Muller et al. (1972)
! From procedure Muller72 in HumanB.cmd
!  Male
  Human
  ResetDoses
```

```
  SET Conc=50.0, CC=.FALSE., TChng=6.0,
Days=1.0, TMax=24.0, TStp=25.0
  START /NC
  PLOT /DATA=muller72a CBldTCA
  PLOT /DATA=muller72b CTCOH
  PLOT /DATA=muller72c AUrnTCOGTCOH
  PLOT /DATA=muller72d AUrnTCA
END

! CBldTCA, TCA data divided by 2,
plasma to whole blood conversion
DATA Muller72a (T, CBldTCA)
   7.0   2.9
  13.0   7.1
  17.0   8.9
END

DATA Muller72b (T, CTCOH)
  16.0   1.7
  20.0   1.3
END

DATA Muller72c (T, AUrnTCOGTCOH)
  24.0   100.8
END

DATA Muller72d (T, AUrnTCA)
  24.0   18.4
END


PROCED Muller74
! Data from Muller et al. (1974)
! From procedure Muller74 in HumanB.cmd
!  Male
  Human
  ResetDoses
  SET Conc=100.0, CC=.FALSE.,
TChng=6.0, Days=1.0, TMax=24.0,
TStp=75.0
  START /NC
  PLOT /DATA=muller74a CVen
  PLOT /DATA=muller74b CTCOH
  PLOT /DATA=muller74c CBldTCA
  PLOT /DATA=muller74d CAlvPPM
  PLOT /DATA=muller74e AUrnTCOGTCOH
  PLOT /DATA=muller74f AUrnTCA
END

! TCA data divided by 2 to account for
plasma
DATA Muller74a (T, CVen)
   0.97   0.67
   1.92   1.05
   3.0    0.93
   3.97   0.83
   5.00   1.02
   5.95   1.02
   6.38   0.72
   6.53   0.52
   7.98   0.31
   8.99   0.21
  10.0    0.18
END

DATA Muller74b (T, CTCOH)
   0.97   0.76
   1.92   1.74
   3.0    2.51
   3.97   3.43
   5.00   4.18
   5.95   5.75
   6.38   5.02
   6.53   4.47
   7.98   4.42
   8.99   3.54
  10.0    3.59
  12.0    3.03
  14.0    2.61
  24.5    1.24
  35.59   0.8
  48.5    0.33
END

DATA Muller74c (T, CBldTCA)
   0.97    1.2
   1.92    3.8
   3.97    5.9
   5.95    9.4
   7.98   13.1
  10.0    14.3
  12.0    16.7
  14.0    19.1
  24.5    23.3
  35.59   21.8
  48.5    19.7
  59.5    18.7
END

DATA Muller74d (T, CAlvPPM)
   0.97    9.0
   1.92    9.0
   3.0    13.44
   3.97   14.27
   5.00   18.34
   5.95   14.06
   6.38    5.37
   6.53    3.94
   7.98    2.52
   8.99    1.5
  10.0     0.76
  12.0     0.37
END

DATA Muller74e (T, AUrnTCOGTCOH)
  24.5   244.8
  48.5   300.8
  72.0   315.9
END

DATA Muller74f (T, AUrnTCA)
  24.5    43.2
  48.5    88.1
  72.0   133.5
END
```

```
PROCED StewartParam
  SET VMaxC=5.0
END

PROCED Stewart
! Data from Stewart et al. (1970)
! From procedures AF6A, AF6B, and AF6C
in TCENew.cmd
! 200 ppm TCE -- Human
  Human
  ResetDoses
  SET ZZXERR=39*1.0e-7, ZZMERR=39*1.0e-
7
  StewartParam
  SET Conc=200.0, CC=.FALSE.,
TChng=7.0, Days=5.0, TMax=150.0, ...
      TStp=410.0
  START /NC
  PLOT /DATA=stewart1 CAlvPPM
  PLOT /DATA=stewart2 AUrnTCA
  PLOT /DATA=stewart3 AUrnTCOGTCOH
END

DATA Stewart1 (T, CAlvPPM)
    3.399   10.264
    3.135   75.053
    8.505   10.84
    9.198    8.306
   11.141    5.108
   14.287    3.315
   23.69     1.207
   27.506   10.935
   32.604   11.376
   32.965    9.629
   34.996    4.435
   38.121    2.753
   47.419    1.602
   51.096   75.077
   51.43    11.628
   56.358   12.144
   56.589    8.984
   59.26     3.528
   61.543    2.448
   71.645    1.616
   75.282    8.477
   79.185    8.686
   81.269    7.745
   82.919    3.548
   86.226    2.931
   95.579    1.648
   99.343    8.523
  103.74     8.834
  105.49     8.082
  107.159    3.686
  110.124    2.926
END

DATA Stewart2 (T, AUrnTCA)
   23.928     51.208
   47.574    225.786
   71.475    455.927
   95.852    761.268
  119.615   1154.375
  143.872   1402.376
  168.119   1594.802
  191.701   1713.81
  215.25    1813.51
  239.152   1858.527
  263.597   1927.884
END

DATA Stewart3 (T, AUrnTCOGTCOH)
   24.0    308.0
   48.0    667.0
   72.0   1066.0
   96.0   1604.0
  120.0   2009.0
  144.0   2154.0
  168.0   2303.0
  192.0   2355.0
  216.0   2395.0
  240.0   2410.0
  264.0   2414.0
  336.0   2428.0
  408.0   2442.0
END


PROCED Triebig
! Data from Triebig et al. (1976)
! From procedure Triebig in HumanB.cmd
!  Male
  Human
  ResetDoses
  SET Conc=136.0, CC=.FALSE.,
TChng=6.0, Days=1.0, TMax=24.0,
TStp=25.0
  START /NC
  PLOT /DATA=triebig1 CVen
  PLOT /DATA=triebig2 CTCOH
  PLOT /DATA=triebig3 CBldTCA
  PLOT /DATA=triebig4 CAlvPPM
END

DATA Triebig1 (T, CVen)
   6.0   1.3
END

DATA Triebig2 (T, CTCOH)
   6.0   6.2
  24.0   3.8
END

DATA Triebig3 (T, CBldTCA)
   6.0   12.1
  24.0   32.8
END

DATA Triebig4 (T, CAlvPPM)
   6.0   31.9
  24.0    4.6
END


PROCED M60
```

```
! Data from Fisher et al. (1998)
! Data from procedure M60 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3
  Human
  ResetDoses
  SET BW=71.1, VFatC=0.14
  SET Conc=55.2, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0
  START /NC
  PLOT /DATA=m60a CVen
  PLOT /DATA=m60b CTCOH
  PLOT /DATA=m60c CBldTCA
  PLOT /DATA=m60d AUrnTCA
  PLOT /DATA=m60e AUrnTCOGTCOH
END

DATA M60a (T, CVen)
   0.58   1.89
   0.98   1.36
   2.02   2.68
   3.02   2.67
   4.02   2.79
   4.25   2.42
   4.44   1.52
   5.02   0.82
   5.83   0.37
   8.0    0.29
END

DATA M60b (T, CTCOH)
   0.58   0.63
   0.98   1.07
   2.02   1.57
   3.02   1.90
   4.02   1.94
   4.25   2.02
   4.44   2.26
   5.02   1.02
   5.83   0.96
   8.0    1.65
  10.0    1.38
  12.0    1.26
  14.17   1.13
  16.02   1.03
  18.02   1.05
  20.0    0.90
END

DATA M60c (T, CBldTCA)
   0.58   0.43
   0.98   0.55
   2.02   1.07
   3.02   1.57
   4.02   1.96
   4.25   2.01
   4.44   2.19
   5.02   2.28
   5.83   2.52
   8.0    2.92
  10.0    3.20
  12.0    3.56
  14.17   4.19
  16.02   3.90
  18.02   4.95
  20.0    5.04
  22.0    5.08
  44.83   5.51
  68.72   9.45
  93.12   4.27
END

DATA M60d (T, AUrnTCA)
   0.5    0.002
   3.12   0.082
   4.63   0.184
   5.45   0.249
   6.45   0.307
   8.13   0.539
  10.17   0.852
  12.15   1.35
  14.27   1.78
  16.13   2.12
  18.15   2.48
  20.2    2.89
  22.22   3.48
  24.22   4.28
  32.85   5.35
  34.22   5.66
  39.85   6.72
  44.25   7.42
  47.25   8.14
  52.13   8.93
  58.59  10.17
  67.75  11.19
  72.37  12.56
  77.15  13.78
  82.92  14.44
  91.83  15.63
END

DATA M60e (T, AUrnTCOGTCOH)
   0.5    0.0
   3.12   8.24
   4.63  11.60
   5.45  13.64
   6.45  15.64
   8.13  19.73
  10.17  23.26
  12.15  28.95
  14.27  28.95
  16.13  29.79
  18.15  32.07
  20.2   34.21
  22.22  38.49
  24.22  43.06
  32.85  47.48
  34.22  48.60
  39.85  52.15
  44.25  53.88
  47.25  55.21
  52.13  57.21
  58.59  59.15
  67.75  60.89
  72.37  61.46
  77.15  61.84
```

```
  82.92   62.20
  91.83   62.56
END


PROCED M50_1
! Data from Fisher et al. (1998)
! Data from procedure M50_1 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3
  Human
  ResetDoses
  SET BW=52.3, VFatC=0.1
  SET Conc=53.1, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
  START /NC
  PLOT /DATA=m50_1a CVen
  PLOT /DATA=m50_1b CTCOH
  PLOT /DATA=m50_1c CBldTCA
  PLOT /DATA=m50_1d AUrnTCA
  PLOT /DATA=m50_1e AUrnTCOGTCOH
END

DATA M50_1a (T, CVen)
    0.5     0.67
    1.0     1.37
    2.03    1.96
    3.0     1.92
    4.02    2.08
    4.25    1.13
    4.5     0.76
    5.02    0.42
    6.02    0.30
    8.08    0.21
   10.0     0.15
END

DATA M50_1b (T, CTCOH)
    1.0     0.43
    2.03    1.20
    3.0     1.26
    4.02    1.69
    4.25    1.66
    4.5     1.60
    5.02    1.58
    6.02    1.51
    8.08    1.44
   10.0     1.52
   12.0     1.14
   14.0     1.05
   16.0     1.04
   18.0     1.06
   20.0     0.45
   22.0     0.75
END

DATA M50_1c (T, CBldTCA)
    1.0     0.29
    2.03    0.77
    3.0     1.33
    4.02    1.84
    4.25    1.93
    4.5     2.07
```

```
    5.02    2.27
    6.02    2.94
    8.08    3.58
   10.0     3.72
   12.0     3.98
   14.0     4.40
   16.0     4.58
   18.0     4.86
   20.0     5.73
   22.0     4.22
   44.78    5.00
   68.72    4.72
  100.4     4.47
END

DATA M50_1d (T, AUrnTCA)
    5.25     1.00
    5.97     1.53
    8.0      3.34
   10.17     6.01
   12.17     7.60
   14.17    13.02
   16.17    14.83
   18.17    16.67
   20.17    18.69
   22.17    21.30
   25.0     21.95
   29.83    26.24
   37.83    31.79
   44.83    40.44
   45.67    40.86
   49.67    42.64
   53.33    42.94
   61.23    43.80
   62.83    44.54
   79.1     48.73
END

DATA M50_1e (T, AUrnTCOGTCOH)
    5.25     5.26
    5.97     8.23
    8.0     13.05
   10.17    16.30
   12.17    19.05
   14.17    24.62
   16.17    26.97
   18.17    29.06
   20.17    30.62
   22.17    32.53
   25.0     33.35
   29.83    35.43
   37.83    37.99
   44.83    38.21
   45.67    39.06
   49.67    39.63
   53.33    39.70
   61.23    39.90
   62.83    40.23
   79.1     40.67
END


PROCED M50_2
```

```
! Data from Fisher et al. (1998)
! Data from procedure M50_2 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3
  Human
  ResetDoses
  SET BW=69.3, VFatC=0.27
  SET Conc=49.3, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0
  START /NC
  PLOT /DATA=m50_2a CVen
  PLOT /DATA=m50_2b CTCOH
  PLOT /DATA=m50_2c CBldTCA
  PLOT /DATA=m50_2d AUrnTCA
  PLOT /DATA=m50_2e AUrnTCOGTCOH
END

DATA M50_2a (T, CVen)
   0.5    0.61
   1.0    0.74
   2.0    1.11
   3.0    1.01
   4.0    1.05
   4.25   0.81
   4.5    0.46
END

DATA M50_2b (T, CTCOH)
   0.5    0.44
   1.0    0.55
   2.0    0.83
   3.0    1.08
   4.0    1.35
   4.25   1.26
   4.5    1.34
   5.0    1.11
   6.0    1.01
   8.0    0.9
  10.0    0.76
  14.0    0.66
  16.0    0.63
  18.0    0.56
  20.0    0.51
END

DATA M50_2c (T, CBldTCA)
   0.5    0.29
   1.0    0.65
   2.0    1.47
   3.0    2.27
   4.0    2.91
   4.25   2.99
   4.5    3.12
   5.0    3.49
   6.0    3.66
   8.0    4.29
  10.0    4.69
  12.0    5.11
  14.0    5.17
  16.0    5.26
  18.0    5.66
  20.0    5.18
  22.0    5.69
  49.08   6.67
  71.72   6.49
  97.47   6.01
END

DATA M50_2d (T, AUrnTCA)
   4.55   0.041
   5.08   0.062
   6.06   0.15
   8.08   0.26
  10.06   0.41
  12.08   0.53
  14.08   0.65
  16.08   0.80
  18.08   0.92
  20.08   1.05
  22.17   1.18
  31.33   1.46
  49.0    2.20
  64.33   3.61
  77.0    4.36
  86.25   5.03
END

DATA M50_2e (T, AUrnTCOGTCOH)
   4.55    8.45
   5.08   15.20
   6.06   21.60
   8.08   28.09
  10.06   35.67
  12.08   39.98
  14.08   43.78
  16.08   47.68
  18.08   50.54
  20.08   53.03
  22.17   55.30
  31.33   60.62
  49.0    69.80
  64.33   73.15
  77.0    74.82
  86.25   76.02
END


PROCED F50_1
! Data from Fisher et al. (1998)
! Data from procedure F50_1 (in Bld50_F
and Urin50_F) in HumanB.cmd
! Female 50 ppm exposure, n=2
  Human
  ResetDoses
  SET BW=62.3, VFatC=0.24
  SET Conc=53.0, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
  START /NC
  PLOT /DATA=f50_1a CVen
  PLOT /DATA=f50_1b CTCOH
  PLOT /DATA=f50_1c CBldTCA
  PLOT /DATA=f50_1d AUrnTCA
  PLOT /DATA=f50_1e AUrnTCOGTCOH
END

DATA F50_1a (T, CVen)
```

```
    0.5     0.93
    1.0     1.33
    2.0     1.65
    3.0     1.85
    4.0     1.45
    4.27    0.94
    4.55    0.63
    5.10    0.32
    6.0     0.18
END

DATA F50_1b (T, CTCOH)
    1.0     0.33
    2.0     0.63
    3.0     0.79
    4.0     0.98
    4.27    0.83
    4.55    0.83
    5.10    0.90
    6.0     0.89
    8.0     0.76
   10.0     0.66
   12.0     0.67
   14.0     0.54
   16.05    0.48
   18.0     0.47
   22.0     0.35
END

DATA F50_1c (T, CBldTCA)
    1.0     0.38
    2.0     1.23
    3.0     1.96
    4.0     2.80
    4.27    2.81
    4.55    3.23
    5.10    3.34
    6.0     3.72
    8.0     4.88
   10.0     4.93
   12.0     5.28
   14.0     5.18
   16.05    5.37
   18.0     6.03
   20.02    4.87
   22.0     6.66
   44.92    6.66
   68.86    5.27
  100.44    2.27
END

DATA F50_1d (T, AUrnTCA)
   5.25     1.35
   5.97     4.49
   8.0      7.17
  10.17     9.38
  12.17    10.36
  14.17    11.91
  16.17    13.46
  18.17    14.70
  20.17    15.64
  22.17    16.49
  25.0     22.11
  29.83    23.27
  37.83    26.03
  44.83    27.35
  49.67    33.94
  53.33    35.83
  61.23    42.58
  62.83    43.36
  67.92    50.68
  75.75    52.36
  79.63    53.79
  96.67    54.16
  96.92    55.93
END

DATA F50_1e (T, AUrnTCOGTCOH)
   5.25     4.42
   5.97     6.71
   8.0     12.00
  10.17    15.40
  12.17    16.73
  14.17    20.35
  16.17    23.49
  18.17    25.44
  20.17    25.44
  22.17    26.96
  25.0     30.55
  29.83    32.71
  37.83    34.38
  44.83    34.88
  49.67    37.25
  53.33    38.53
  61.23    41.16
  62.83    41.38
  67.92    43.01
  75.75    43.29
  79.63    43.53
  96.67    43.66
  96.92    43.85
END


PROCED F60_1
! Data from Fisher et al. (1998)
! Data from procedure F60_1 (in Bld50_F
and Urin50_F) in HumanB.cmd
! Female 50 ppm exposure, n=2
  Human
  ResetDoses
  SET BW=66.5, VFatC=0.32
  SET Conc=55.1, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0
  START /NC
  PLOT /DATA=f60_1a CVen
  PLOT /DATA=f60_1b CTCOH
  PLOT /DATA=f60_1c CBldTCA
  PLOT /DATA=f60_1d AUrnTCA
  PLOT /DATA=f60_1e AUrnTCOGTCOH
END

DATA F60_1a (T, CVen)
   0.58    1.00
   1.02    1.29
   2.0     1.38
```

```
   3.0    1.70
   4.0    1.72
   4.25   1.08
   4.47   1.17
   5.0    0.55
   6.0    0.39
   8.03   0.22
END

DATA F60_1b (T, CTCOH)
   0.58   0.32
   1.02   0.49
   2.0    0.85
   3.0    0.97
   4.0    1.20
   4.25   1.14
   4.47   1.18
   5.0    1.13
   9.98   0.70
  12.0    0.60
  14.02   0.52
  16.0    0.55
  18.03   0.54
  20.0    0.45
  22.0    0.35
END

DATA F60_1c (T, CBldTCA)
   0.58   0.16
   1.02   0.46
   2.0    1.15
   3.0    1.53
   4.0    1.90
   4.25   2.10
   4.47   2.18
   5.0    2.13
   6.0    2.56
   8.03   3.32
   9.98   2.83
  12.0    2.98
  14.02   3.42
  16.0    3.44
  18.03   3.31
  20.0    4.15
  22.0    4.07
  44.33   3.70
  68.32   3.31
  93.38   1.02
END

DATA F60_1d (T, AUrnTCA)
   4.58    0.64
   5.26    0.76
   6.12    0.85
   8.12    1.83
  10.18    2.57
  12.18    3.36
  14.32    3.94
  16.18    5.12
  18.16    6.03
  20.25    6.67
  22.53    7.30
  23.25    7.60
  25.25    7.96
  27.58    8.60
  29.5     8.89
  30.92    9.21
  32.92    9.86
  35.0     9.66
  39.83   11.19
  42.0    11.85
  43.08   12.35
  44.72   12.73
  46.5    13.49
  49.83   14.31
  52.00   15.73
  53.59   16.12
  54.53   16.34
  56.83   16.93
  58.5    17.24
  59.25   17.85
  63.83   18.13
  68.28   18.53
  70.67   19.18
  72.78   19.42
  74.75   20.00
  76.92   20.58
  80.33   20.79
  81.50   20.93
  82.42   21.82
  83.5    21.37
  90.25   21.56
  91.42   21.69
  92.33   21.87
END

DATA F60_1e (T, AUrnTCOGTCOH)
   4.58   20.08
   5.26   22.91
   6.12   24.87
   8.12   28.94
  10.18   36.46
  12.18   39.14
  14.32   42.64
  16.18   45.16
  18.16   53.64
  20.25   56.34
  22.53   57.08
  23.25   57.64
  25.25   58.45
  27.58   60.33
  29.5    61.44
  30.92   62.83
  32.92   67.36
  35.0    68.30
  39.83   69.92
  42.0    70.88
  43.08   71.09
  44.72   71.59
  46.5    71.99
  49.83   72.60
  52.00   73.60
  53.59   73.93
  54.53   74.27
  56.83   74.26
  58.5    74.56
```

```
  59.25   74.71
  63.83   74.77
  68.28   75.16
  70.67   75.34
  72.78   75.52
  74.75   75.75
  76.92   75.81
  80.33   76.05
  81.50   76.06
  82.42   76.12
  83.5    76.15
  90.25   76.30
  91.42   76.34
  92.33   76.39
END


PROCED M100_1
! Data from Fisher et al. (1998)
! Data from procedure M100_1 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=71.4, VFatC=0.17
  SET Conc=105.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=m100_1a CVen
  PLOT /DATA=m100_1b CTCOH
  PLOT /DATA=m100_1c CBldTCA
  PLOT /DATA=m100_1d AUrnTCA
  PLOT /DATA=m100_1e AUrnTCOGTCOH
END

DATA M100_1a (T, CVen)
   0.52   1.98
   1.0    2.69
   2.0    3.38
   3.0    3.76
   4.0    3.95
   4.25   3.26
   4.5    2.54
   5.0    1.12
   6.0    0.72
   8.0    0.52
  10.0    0.31
  12.0    0.28
  14.0    0.23
  16.0    0.17
  18.0    0.15
END

DATA M100_1b (T, CTCOH)
   1.0    0.39
   2.0    1.30
   3.0    2.18
   4.0    2.83
   4.25   2.94
   4.5    3.21
   5.0    2.78
   6.0    2.84
   8.0    2.52
  10.0    2.03
  12.0    1.56
  14.0    1.56
  16.0    1.31
  18.0    1.21
  20.03   1.15
END

DATA M100_1c (T, CBldTCA)
   0.52   0.15
   1.0    0.50
   2.0    1.07
   3.0    2.11
   4.0    3.12
   4.25   2.87
   4.5    3.39
   5.0    4.00
   6.0    4.09
   8.0    4.76
  10.0    5.52
  12.0    6.16
  14.0    6.48
  16.0    8.12
  18.0    7.18
  20.03   8.56
  22.02   8.14
  45.83   9.30
  69.74   7.37
  93.75   6.97
END

DATA M100_1d (T, AUrnTCA)
   4.5      1.47
   6.1      2.82
   8.0      5.02
  10.1      7.10
  11.4      8.87
  12.1     10.22
  14.1     12.67
  16.0     15.33
  18.0     16.85
  20.23    22.83
  21.97    25.23
  26.0     30.03
  31.5     33.10
  34.25    39.59
  35.5     42.21
  36.75    48.47
  44.75    52.39
  52.0     55.28
  54.5     58.64
  56.5     59.80
  59.5     62.40
  60.5     65.00
  68.5     79.17
  70.25    83.51
  73.00    88.15
  79.5     99.19
  81.5    100.11
  84.67   100.62
END
```

```
DATA M100_1e (T, AUrnTCOGTCOH)
   4.5      13.94
   6.1      23.22
   8.0      30.95
  10.1      37.58
  11.4      43.49
  12.1      46.17
  14.1      50.32
  16.0      56.69
  18.0      61.37
  20.23     65.35
  21.97     68.94
  26.0      74.63
  31.5      79.76
  34.25     82.89
  35.5      84.29
  36.75     86.91
  44.75     90.23
  52.0      91.80
  54.5      93.75
  56.5      94.88
  59.5      96.10
  60.5      96.99
  68.5      99.59
  70.25    100.64
  73.00    102.16
  79.5     104.07
  81.5     104.74
  84.67    104.94
END


PROCED M100_2
! Data from Fisher et al. (1998)
! Data from procedure M100_2 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=82.3, VFatC=0.14
  SET Conc=105.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=m100_2a CVen
  PLOT /DATA=m100_2b CTCOH
  PLOT /DATA=m100_2c CBldTCA
  PLOT /DATA=m100_2d CDCA
  PLOT /DATA=m100_2e AUrnTCA
  PLOT /DATA=m100_2f AUrnTCOGTCOH
END

DATA M100_2a (T, CVen)
   0.52   1.69
   1.0    2.50
   2.02   3.50
   3.02   4.24
   4.02   4.75
   4.27   3.76
   4.52   2.20
   5.02   0.96
   6.42   0.53
   8.0    0.26
  10.0    0.17
  12.0    0.17
END

DATA M100_2b (T, CTCOH)
   1.0    0.37
   2.02   1.41
   3.02   2.40
   4.02   3.59
   4.27   4.16
   4.52   3.73
   5.02   3.65
   6.42   3.63
   8.0    2.60
  10.0    2.82
  12.0    1.84
  14.0    1.55
  16.0    1.59
  18.0    1.06
  20.0    1.23
  22.03   0.75
END

DATA M100_2c (T, CBldTCA)
   0.52   0.24
   1.0    0.60
   2.02   1.24
   3.02   2.71
   4.27   4.23
   4.52   3.86
   5.02   3.92
   6.42   4.54
   8.0    5.71
  10.0    6.21
  14.0    7.96
  16.0    9.08
  18.0    8.30
  20.0    8.43
  22.03   8.95
  69.72   5.51
  93.61   3.55
END

DATA M100_2d (T, CDCA)
   0.52   0.004
   1.0    0.004
   2.02   0.004
   3.02   0.004
   4.27   0.005
   8.0    0.007
END

DATA M100_2e (T, AUrnTCA)
   4.38     1.74
   6.0      2.77
   8.0      3.94
  10.0      5.52
  12.0      7.66
  14.0      9.62
  16.0     11.69
  18.0     13.57
  20.0     20.39
  22.0     26.25
```

```
   24.42     30.32
   31.0      40.91
   35.42     50.70
   44.90     65.02
   49.75     65.02
   53.75     78.15
   54.76     79.79
   59.42     83.82
   68.9      93.09
   70.83     98.82
   72.0     100.66
   74.58    112.13
   77.0     117.83
   83.92    118.82
   86.0     119.30
   92.67    120.02
END

DATA M100_2f (T, AUrnTCOGTCOH)
    6.0      8.69
    8.0     18.39
   10.0     27.48
   12.0     37.49
   14.0     44.58
   16.0     51.78
   18.0     56.11
   20.0     60.47
   22.0     64.77
   24.42    66.98
   31.0     75.49
   35.42    79.43
   44.90    82.13
   49.75    85.29
   53.75    88.15
   54.76    88.66
   59.42    89.44
   68.9     90.60
   70.83    91.71
   72.0     91.84
   74.58    92.37
   77.0     93.07
   83.92    93.79
   86.0     94.17
   92.67    94.55
END


PROCED M100_3
! Data from Fisher et al. (1998)
! Data from procedure M100_3 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=82.7, VFatC=0.14
  SET Conc=102.6, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=m100_3a CVen
  PLOT /DATA=m100_3b CTCOH
  PLOT /DATA=m100_3c CBldTCA
  PLOT /DATA=m100_3d AUrnTCA
  PLOT /DATA=m100_3e AUrnTCOGTCOH
END

DATA M100_3a (T, CVen)
   0.5     1.93
   1.07    2.34
   2.0     2.84
   3.0     3.40
   3.98    3.41
   4.25    2.20
   4.5     1.66
   5.0     0.89
   6.0     0.38
END

DATA M100_3b (T, CTCOH)
   0.5     0.45
   1.07    0.77
   2.0     1.51
   3.0     2.41
   3.98    3.3
   4.25    3.64
   4.5     3.67
   5.0     3.48
   6.0     3.05
   8.0     2.52
  10.02    2.38
  12.0     2.16
  14.0     1.73
  16.02    1.48
  18.07    1.12
  20.0     1.01
  22.0     0.85
END

DATA M100_3c (T, CBldTCA)
   0.5     0.23
   1.07    0.49
   2.0     1.07
   3.0     1.89
   3.98    2.87
   4.25    3.69
   4.5     3.87
   5.0     3.59
   6.0     4.18
   8.0     4.71
  10.02    5.46
  12.0     5.67
  14.0     5.97
  16.02    6.05
  18.07    6.22
  20.0     7.54
  22.0     7.26
  46.85    8.43
  71.47    3.86
  95.50    3.55
END

DATA M100_3d (T, AUrnTCA)
   3.03     0.488
   4.75     0.961
   6.7      2.09
   8.25     2.96
```

```
  10.17    5.56
  12.08    7.17
  14.19    8.37
  15.58    9.09
  17.6     9.70
  18.23   10.13
  19.58   10.99
  20.05   11.24
  21.33   11.88
  22.17   12.36
  23.2    13.03
  35.42   14.18
  40.67   16.14
  46.67   18.07
  47.17   19.06
  52.33   20.35
  55.25   23.68
  68.17   24.71
  69.75   27.02
END

DATA M100_3e (T, AUrnTCOGTCOH)
   3.03    32.70
   4.75    60.26
   6.7     97.98
   8.25   130.67
  10.17   182.90
  12.08   204.64
  14.19   224.53
  15.58   233.79
  17.6    240.99
  18.23   245.36
  19.58   253.46
  20.05   255.90
  21.33   261.17
  22.17   265.40
  23.2    269.76
  35.42   271.64
  40.67   276.15
  46.67   277.54
  47.17   277.83
  52.33   278.12
  55.25   278.81
  68.17   278.88
  69.75   279.07
END


PROCED M100_4
! Data from Fisher et al. (1998)
! Data from procedure M100_4 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=71.1, VFatC=0.14
  SET Conc=101.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=m100_4a CVen
  PLOT /DATA=m100_4b CTCOH
  PLOT /DATA=m100_4c CBldTCA
  PLOT /DATA=m100_4d AUrnTCA
  PLOT /DATA=m100_4e AUrnTCOGTCOH
END

DATA M100_4a (T, CVen)
   0.5    3.10
   1.0    3.76
   2.0    3.46
   3.0    3.83
   4.02   3.78
   4.25   2.90
   4.5    2.11
   5.0    1.09
END

DATA M100_4b (T, CTCOH)
   0.5    0.56
   1.0    1.12
   2.0    1.75
   3.0    2.55
   4.02   3.48
   4.25   3.73
   4.5    3.52
   5.0    3.78
   6.0    3.79
   8.0    3.30
  10.0    2.96
  12.05   2.71
  14.0    2.38
  16.0    2.04
  18.0    1.89
  20.0    1.57
  22.05   1.40
END

DATA M100_4c (T, CBldTCA)
   0.5    0.3
   1.0    0.75
   2.0    1.42
   3.0    2.34
   4.02   3.01
   4.25   2.58
   4.5    3.10
   5.0    3.26
   6.0    4.21
   8.0    4.99
  10.0    5.46
  12.05   5.74
  14.0    6.69
  16.0    6.85
  18.0    7.14
  20.0    9.85
  22.05   9.32
  50.52   8.87
  74.03   8.08
  98.58   3.82
END

DATA M100_4d (T, AUrnTCA)
   4.35    0.98
   5.03    1.21
   6.07    1.42
   8.07    2.05
```

```
  10.04    3.12
  12.07    3.60
  14.06    4.09
  16.03    4.57
  18.02    4.86
  20.04    5.28
  22.13    5.98
  25.5     8.14
  36.5     8.94
  44.1    10.97
  47.0    11.58
  54.0    13.48
  61.45   15.33
  69.3    17.47
  85.0    21.65
  93.55   21.65
END

DATA M100_4e (T, AUrnTCOGTCOH)
   4.35    28.92
   5.03    31.85
   6.07    40.01
   8.07    56.31
  10.04    68.48
  12.07    78.80
  14.06    89.82
  16.03    98.66
  18.02   105.25
  20.04   112.29
  22.13   122.73
  25.5    141.62
  36.5    150.29
  44.1    162.32
  47.0    165.74
  54.0    173.84
  61.45   178.30
  69.3    182.24
  85.0    185.01
  93.55   186.89
END


PROCED M100_5
! Data from Fisher et al. (1998)
! Data from procedure M100_5 (in Bld_M,
Exh_M and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=73.2, VFatC=0.18
  SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=110.0
  START /NC
  PLOT /DATA=m100_5a CVen
  PLOT /DATA=m100_5b CTCOH
  PLOT /DATA=m100_5c CBldTCA
  PLOT /DATA=m100_5d CAlvPPM
  PLOT /DATA=m100_5e AUrnTCA
  PLOT /DATA=m100_5f AUrnTCOGTCOH
END

DATA M100_5a (T, CVen)
    0.5     0.76
    1.0     0.86
    2.0     1.15
    3.0     1.15
    4.0     1.23
    4.25    0.77
    4.53    0.46
    5.0     0.34
    6.0     0.21
    8.0     0.15
END

DATA M100_5b (T, CTCOH)
    1.0     0.52
    2.0     1.35
    3.0     1.87
    4.0     2.50
    4.25    2.59
    4.53    2.58
    5.0     2.25
    6.0     2.15
    8.0     1.98
   10.0     1.56
   12.0     1.02
   14.0     1.26
   16.03    0.89
   18.0     0.79
   20.0     0.73
   22.0     0.70
END

DATA M100_5c (T, CBldTCA)
    0.5     0.11
    1.0     0.36
    2.0     1.07
    3.0     1.55
    4.0     2.31
    4.25    2.03
    4.53    2.16
    5.0     2.35
    6.0     2.53
    8.0     3.61
   10.0     3.93
   12.0     4.57
   14.0     4.50
   16.03    5.02
   18.0     5.10
   20.0     5.07
   22.0     5.91
   51.0     6.38
   78.08    5.33
  100.83    4.01
END

DATA M100_5d (T, CAlvPPM)
    4.0     12.386
    4.25     3.305
    4.53     2.478
    5.0      1.567
    6.0      0.577
    8.0      0.317
   10.0      0.286
END
```

```
DATA M100_5e (T, AUrnTCA)
   4.67    1.36
   5.05    1.66
   6.3     2.70
   8.05    4.22
  10.07    6.04
  12.07    8.04
  14.07   10.37
  16.15   13.33
  18.08   16.55
  20.05   20.04
  22.15   23.89
  25.33   30.02
  31.92   35.07
  35.33   38.42
  43.58   43.06
  51.08   46.65
  53.25   48.88
  56.92   54.83
  58.33   57.31
  59.67   59.49
  63.75   62.36
  67.42   66.44
  73.08   70.15
  78.0    73.57
  80.58   75.42
  82.75   77.73
  84.25   78.87
  84.92   80.37
  87.58   83.60
  91.83   86.81
END

DATA M100_5f (T, AUrnTCOGTCOH)
   4.67   16.05
   5.05   18.22
   6.3    25.28
   8.05   34.46
  10.07   43.49
  12.07   49.91
  14.07   55.78
  16.15   59.33
  18.08   65.07
  20.05   68.36
  22.15   71.48
  25.33   76.10
  31.92   81.25
  35.33   83.82
  43.58   86.11
  51.08   87.66
  53.25   88.38
  56.92   89.39
  58.33   89.71
  59.67   89.92
  63.75   89.92
  67.42   90.38
  73.08   91.07
  78.0    91.55
  80.58   91.79
  82.75   91.94
  84.25   92.03
  84.92   92.22
  87.58   92.37
  91.83   92.55
END


PROCED M100_6
! Data from Fisher et al. (1998)
! Data from procedure M100_6 (in Bld_M,
Exh_M and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=52.3, VFatC=0.06
  SET Conc=97.8, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
  START /NC
  PLOT /DATA=m100_6a CVen
  PLOT /DATA=m100_6b CTCOH
  PLOT /DATA=m100_6c CBldTCA
  PLOT /DATA=m100_6d CAlvPPM
  PLOT /DATA=m100_6e AUrnTCA
  PLOT /DATA=m100_6f AUrnTCOGTCOH
END

DATA M100_6a (T, CVen)
    0.5    0.64
    1.0    0.94
    2.02   1.35
    3.0    1.62
    4.02   1.56
    4.25   1.16
    4.5    0.77
    5.0    0.37
    6.0    0.23
    8.0    0.19
   10.03   0.17
END

DATA M100_6b (T, CTCOH)
    1.0    0.47
    2.02   1.10
    3.0    1.58
    4.02   2.10
    4.25   2.21
    4.5    2.20
    5.0    2.15
    6.0    1.94
    8.0    1.88
   10.03   1.61
   12.02   1.39
   14.03   1.26
   16.0    1.06
   18.0    0.95
   19.97   0.88
   22.07   0.77
END

DATA M100_6c (T, CBldTCA)
    0.5    0.21
    1.0    0.49
    2.02   1.10
    3.0    1.67
    4.02   2.52
```

```
    4.25     2.44
    4.5      2.71
    5.0      3.18
    6.0      3.46
    8.0      4.26
   10.03     4.93
   12.02     5.43
   14.03     5.85
   16.0      6.02
   18.0      6.18
   19.97     6.35
   22.07     6.52
   48.0     12.88
   71.83     6.25
  101.08     5.07
END

DATA M100_6d (T, CAlvPPM)
    4.02    24.679
    4.25     6.422
    4.5      4.394
    5.0      2.691
    6.0      1.388
    8.0      1.198
   10.03     0.592
   12.02     0.470
   14.03     0.369
   16.0      0.351
END

DATA M100_6e (T, AUrnTCA)
   4.55     0.32
   5.12     0.41
   6.08     1.04
   8.13     1.32
  10.13     2.51
  12.1      4.77
  14.1      7.29
  16.1     10.23
  18.12    11.50
  20.08    13.03
  22.3     14.26
  30.42    17.65
  35.67    18.58
  51.83    18.58
  56.67    18.58
  61.5     18.95
  70.17    20.95
  72.67    22.77
  76.92    25.76
  82.67    30.01
  85.75    30.70
  93.67    34.88
END

DATA M100_6f (T, AUrnTCOGTCOH)
   4.55    11.60
   5.12    13.64
   6.08    18.54
   8.13    25.00
  10.13    33.99
  12.1     42.10
  14.1     50.19
  16.1     60.58
  18.12    64.73
  20.08    70.85
  22.3     77.69
  30.42    79.75
  35.67    80.14
  51.83    80.23
  56.67    80.32
  61.5     80.66
  70.17    81.44
  72.67    82.38
  76.92    82.74
  82.67    83.28
  85.75    83.35
  93.67    83.79
END


PROCED M100_7Param
  SET VMaxC=3.0
END

PROCED M100_7
! Data from Fisher et al. (1998)
! Data from procedure M100_7 (in Bld_M,
Exh_M and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  M100_7Param
  SET BW=60.9, VFatC=0.10
  SET Conc=101.1, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
  START /NC
  PLOT /DATA=m100_7a CVen
  PLOT /DATA=m100_7b CTCOH
  PLOT /DATA=m100_7c CBldTCA
  PLOT /DATA=m100_7d CAlvPPM
  PLOT /DATA=m100_7e CDCA
  PLOT /DATA=m100_7f AUrnTCA
  PLOT /DATA=m100_7g AUrnTCOGTCOH
END

DATA M100_7a (T, CVen)
    0.5      0.59
    1.0      0.85
    2.0      1.1
    3.0      1.04
    4.0      1.18
    4.3      0.64
    4.5      0.42
    5.0      0.19
END

DATA M100_7b (T, CTCOH)
    0.5      0.28
    1.0      0.76
    2.0      1.92
    3.0      1.69
    4.0      2.34
    4.3      2.34
    4.5      2.16
```

```
   5.0      2.13
   6.0      1.95
   8.0      1.61
  10.0      1.33
  12.0      1.58
  14.0      0.84
  16.0      0.77
  18.0      0.57
  20.03     0.76
END

DATA M100_7c (T, CBldTCA)
   0.5      0.36
   1.0      0.84
   2.0      1.73
   3.0      2.60
   4.0      3.42
   4.3      3.90
   4.5      3.67
   5.0      4.47
   6.0      5.00
   8.0      5.95
  10.0      6.74
  12.0      7.12
  14.0      7.75
  16.0      8.22
  18.0      8.17
  20.03     9.01
  49.75    10.66
  73.8      8.6
  95.24     7.46
 264.0      3.13
END

DATA M100_7d (T, CAlvPPM)
   4.0     21.575
   4.03    14.272
   4.05    10.770
   4.08     7.056
   4.167    5.876
   4.3      5.773
   4.5      5.010
   5.0      2.498
   6.0      1.713
   8.0      1.263
  10.0      1.029
  12.0      0.936
  14.0      0.809
  16.0      0.738
  18.0      0.683
END

DATA M100_7e (T, CDCA)
   1.0      0.006
   2.0      0.008
   4.0      0.012
END

DATA M100_7f (T, AUrnTCA)
   4.75     0.93
   7.95     3.02
  14.08     5.95
  16.08     7.07
  18.1      8.28
  20.25     9.63
  24.67    13.46
  29.17    15.73
  32.67    20.11
  35.33    22.71
  38.83    24.07
  44.25    25.60
  49.67    27.51
  55.92    29.60
  58.75    33.36
  68.25    39.61
  73.83    43.70
  75.92    45.78
  77.92    48.52
  81.17    51.21
  82.58    53.54
  92.17    60.72
END

DATA M100_7g (T, AUrnTCOGTCOH)
   4.75     40.71
   7.95     69.81
  14.08     89.76
  16.08     96.80
  18.1     102.69
  20.25    107.93
  24.67    121.30
  29.17    128.51
  32.67    135.51
  35.33    138.05
  38.83    140.20
  44.25    142.48
  49.67    144.47
  55.92    144.96
  58.75    145.55
  68.25    146.67
  73.83    147.09
  75.92    147.25
  77.92    147.38
  81.17    147.50
  82.58    147.62
  92.17    147.98
END


PROCED M100_8
! Data from Fisher et al. (1998)
! Data from procedure M100_8 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
  Human
  ResetDoses
  SET BW=70.9, VFatC=0.18
  SET Conc=103.4, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
  START /NC
  PLOT /DATA=m100_8a CVen
  PLOT /DATA=m100_8b CTCOH
  PLOT /DATA=m100_8c CBldTCA
  PLOT /DATA=m100_8d CDCA
  PLOT /DATA=m100_8e AUrnTCA
```

```
  PLOT /DATA=m100_8f AUrnTCOGTCOH
END

DATA M100_8a (T, CVen)
    0.5     2.69
    1.0     2.98
    2.0     3.51
    3.0     3.58
    4.0     2.88
    4.25    1.96
    4.5     1.53
    5.75    0.81
    6.0     0.52
    8.0     0.32
   10.0     0.27
   12.0     0.24
   14.0     0.22
   16.0     0.22
   18.0     0.20
   20.0     0.16
   22.0     0.16
END

DATA M100_8b (T, CTCOH)
    0.5     0.47
    1.0     0.68
    2.0     1.51
    3.0     3.58
    4.0     2.72
    4.25    2.87
    4.5     2.77
    5.75    2.63
    6.0     2.30
    8.0     1.90
   10.0     1.59
   12.0     1.28
   14.0     1.23
   16.0     1.06
   18.0     0.98
   20.0     0.72
   22.0     0.71
END

DATA M100_8c (T, CBldTCA)
    0.5      0.43
    1.0      1.00
    2.0      2.15
    3.0      3.40
    4.0      4.94
    4.25     5.42
    4.5      5.67
    5.75     5.83
    6.0      5.99
    8.0      7.23
   10.0      7.96
   12.0      8.14
   14.0      8.39
   16.0      8.36
   18.0      8.83
   20.0      8.96
   22.0      9.51
   44.98    10.75
   68.9      9.21
   93.08     7.94
  264.0      1.94
END

DATA M100_8d (T, CDCA)
     2.0     0.004
     3.0     0.010
     4.0     0.008
     4.25    0.005
     4.5     0.005
     5.75    0.004
     8.0     0.005
    16.0     0.005
END

DATA M100_8e (T, AUrnTCA)
    4.58     40.02
    5.03     40.67
    6.03     57.48
    8.05     76.60
   10.03     99.19
   12.03    115.98
   14.07    126.00
   16.05    136.55
   18.03    143.51
   20.02    150.54
   22.08    163.57
   45.42    196.37
   47.42    197.62
   48.92    198.48
   50.42    199.33
   53.92    201.12
   57.33    201.12
   59.17    201.73
   60.92    202.15
   63.92    202.88
   67.92    203.60
   74.58    204.11
   80.25    204.47
   82.42    204.92
   84.33    205.07
   85.58    205.15
   86.92    205.30
END

DATA M100_8f (T, AUrnTCOGTCOH)
    4.58      0.935
    5.03      1.34
    6.03      4.10
    8.05      6.10
   10.03      9.74
   12.03     13.29
   14.07     16.29
   16.05     20.29
   18.03     22.87
   20.02     24.83
   22.08     29.98
   45.42     56.81
   47.42     61.82
   48.92     64.84
   50.42     67.02
   53.92     74.27
   57.33     76.87
```

```
  59.17    78.68
  60.92    61.05
  63.92    88.53
  67.92    90.31
  74.58    92.43
  80.25    95.17
  82.42    97.12
  84.33   100.02
  85.58   100.76
  86.92   103.23
END


PROCED F100_1
! Data from Fisher et al. (1998)
! Data from procedure F100_1 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=57.5, VFatC=0.21
  SET Conc=102.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_1a CVen
  PLOT /DATA=f100_1b CTCOH
  PLOT /DATA=f100_1c CBldTCA
  PLOT /DATA=f100_1d AUrnTCA
  PLOT /DATA=f100_1e AUrnTCOGTCOH
END

DATA F100_1a (T, CVen)
   0.5    1.11
   1.0    1.36
   2.0    2.11
   3.0    1.92
   4.0    2.30
   4.25   1.56
   4.50   1.26
   5.0    0.73
   6.0    0.42
END

DATA F100_1b (T, CTCOH)
   0.5    0.22
   1.0    0.46
   2.0    1.18
   3.0    2.18
   4.0    3.03
   4.25   3.29
   4.50   3.67
   5.0    3.13
   6.0    2.57
   8.0    2.46
  10.0    1.93
  12.0    1.57
  14.0    1.30
  16.05   1.08
  18.0    0.89
  20.02   0.56
  22.02   0.65
  46.17   0.3
END

DATA F100_1c (T, CBldTCA)
   0.5    0.21
   1.0    0.39
   2.0    1.05
   3.0    1.86
   4.0    3.46
   4.25   3.78
   4.50   3.91
   5.0    4.22
   6.0    4.67
   8.0    5.71
  10.0    6.29
  12.0    7.76
  14.0    7.78
  16.05   8.11
  18.0    8.79
  20.02   9.05
  22.02   9.34
  46.17   9.58
  69.83   7.93
  94.67   6.69
END

DATA F100_1d (T, AUrnTCA)
   4.62    0.51
   5.08    0.65
   6.86    1.26
   8.33    1.85
  10.25    2.92
  12.13    3.91
  14.08    4.92
  16.15    5.91
  18.0     5.91
  20.05    7.12
  22.17    9.55
  30.67   15.22
  33.67   17.85
  35.42   19.66
  40.67   24.08
  46.67   26.68
  47.17   27.91
  52.33   30.49
  55.25   35.74
  68.17   35.75
  69.75   36.78
  73.92   37.71
  76.0    41.25
  78.17   45.21
  80.33   46.43
  81.5    47.22
  82.25   47.91
  92.58   49.66
  93.67   50.98
  94.17   51.67
END

DATA F100_1e (T, AUrnTCOGTCOH)
   4.62    44.83
   5.08    52.08
   6.86    77.84
   8.33    89.76
```

```
  10.25   108.58
  12.13   122.65
  14.08   133.38
  16.15   140.85
  18.0    147.19
  20.05   151.76
  22.17   155.86
  30.67   169.38
  33.67   174.67
  35.42   175.78
  40.67   179.31
  46.67   179.77
  47.17   179.97
  52.33   180.44
  55.25   181.52
  68.17   184.09
  69.75   184.16
  73.92   184.26
  76.0    184.70
  78.17   185.20
  80.33   185.35
  81.5    185.42
  82.25   185.51
  92.58   185.81
  93.67   185.91
  94.17   185.95
END


PROCED F100_2
! Data from Fisher et al. (1998)
! Data from procedure F100_2 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=66.6, VFatC=0.32
  SET Conc=101.4, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_2a CVen
  PLOT /DATA=f100_2b CTCOH
  PLOT /DATA=f100_2c CBldTCA
  PLOT /DATA=f100_2d AUrnTCA
  PLOT /DATA=f100_2e AUrnTCOGTCOH
END

DATA F100_2a (T, CVen)
   0.5    1.18
   1.0    2.17
   2.0    2.30
   3.0    2.41
   4.0    2.65
   4.23   1.84
   4.5    1.17
   5.0    0.62
   6.0    0.38
END

DATA F100_2b (T, CTCOH)
   1.0    0.74
   2.0    1.38
   3.0    1.93
   4.0    2.41
   4.23   2.40
   4.5    2.33
   5.0    2.17
   6.0    1.94
   8.05   1.81
  10.0    1.38
  12.0    1.17
  14.02   1.25
  16.0    1.01
  18.0    0.88
  20.0    0.74
  22.02   0.70
END

DATA F100_2c (T, CBldTCA)
   2.0    0.91
   3.0    1.75
   4.0    2.65
   4.23   2.54
   4.5    2.65
   5.0    2.73
   6.0    3.26
   8.05   3.58
  10.0    4.50
  12.0    4.02
  14.02   4.17
  16.0    4.45
  18.0    4.90
  20.0    5.26
  22.02   5.94
  46.70   6.68
  70.25   5.20
  93.72   3.60
END

DATA F100_2d (T, AUrnTCA)
   4.37    0.31
   5.03    0.39
   6.1     0.64
   8.1     1.21
  10.07    1.66
  12.03    2.16
  14.1     2.96
  16.05    3.66
  18.05    4.37
  20.06    5.44
  22.15    6.66
  24.32    7.63
  27.05    8.16
  28.3     8.71
  30.1    10.30
  32.45   10.92
  34.2    11.77
  36.1    12.45
  43.2    13.71
  45.4    14.04
  48.0    15.07
  51.4    15.98
  54.05   16.51
  56.4    17.0
  58.2    17.60
```

```
  59.55   19.57
  67.55   19.76
  70.20   20.25
  72.20   21.31
  75.0    22.08
  77.55   22.65
  81.55   24.79
  84.1    30.86
  89.1    31.05
  91.35   31.06
END

DATA F100_2e (T, AUrnTCOGTCOH)
   4.37    35.78
   5.03    44.40
   6.1     54.40
   8.1     72.58
  10.07    90.61
  12.03   104.44
  14.1    116.90
  16.05   127.49
  18.05   127.49
  20.06   136.49
  22.15   144.45
  24.32   147.89
  27.05   150.61
  28.3    154.52
  30.1    157.72
  32.45   160.74
  34.2    163.47
  36.1    165.86
  43.2    167.54
  45.4    168.21
  48.0    169.24
  51.4    170.26
  54.05   171.66
  56.4    172.85
  58.2    173.70
  59.55   175.02
  67.55   175.31
  70.20   175.67
  72.20   176.21
  75.0    176.60
  77.55   177.07
  81.55   178.04
  84.1    178.43
  89.1    178.65
  91.35   178.94
END


PROCED F100_3
! Data from Fisher et al. (1998)
! Data from procedure F100_3 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=55.5, VFatC=0.23
  SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_3a CVen
  PLOT /DATA=f100_3b CTCOH
  PLOT /DATA=f100_3c CBldTCA
  PLOT /DATA=f100_3d AUrnTCA
  PLOT /DATA=f100_3e AUrnTCOGTCOH
END

DATA F100_3a (T, CVen)
   0.58   0.81
   1.0    0.88
   2.0    1.09
   3.0    1.03
   4.0    1.13
   4.17   0.59
   4.5    0.47
   5.0    0.30
   6.0    0.18
   8.02   0.15
END

DATA F100_3b (T, CTCOH)
   0.58   0.33
   1.0    0.57
   2.0    1.01
   3.0    1.25
   4.0    1.79
   4.17   1.64
   4.5    1.54
   5.0    1.43
   6.0    1.27
   8.02   0.95
  10.02   1.01
  12.02   0.90
  14.03   0.88
  16.0    0.74
  18.0    0.69
  20.0    0.63
  22.0    0.61
END

DATA F100_3c (T, CBldTCA)
   0.58    0.40
   1.0     0.97
   2.0     1.72
   3.0     2.64
   4.0     3.41
   4.17    3.62
   4.5     3.86
   5.0     4.39
   6.0     4.80
   8.02    5.73
  10.02    6.79
  12.02    7.55
  14.03    7.68
  16.0     7.98
  18.0     9.27
  20.0     8.91
  22.0     9.12
  46.08   11.31
  75.67   10.49
  94.25    8.47
END
```

```
DATA F100_3d (T, AUrnTCA)
   4.58    0.44
   6.03    0.71
   8.12    1.31
  10.08    2.28
  12.1     3.48
  14.1     4.64
  16.05    5.64
  18.1     6.76
  20.05    7.66
  21.92    8.89
  26.17   10.64
  33.25   13.81
  37.92   14.11
  44.92   15.44
  49.0    16.00
  54.92   23.2
  58.42   22.4
  61.42   24.1
  66.42   29.1
  70.67   32.6
  74.75   36.2
  80.42   36.8
  82.42   37.5
  84.92   37.79
  93.42   45.72
END

DATA F100_3e (T, AUrnTCOGTCOH)
   4.58   12.63
   6.03   17.83
   8.12   26.05
  10.08   30.40
  12.1    36.72
  14.1    41.26
  16.05   44.27
  18.1    47.94
  20.05   50.31
  21.92   53.17
  26.17   57.90
  33.25   65.27
  37.92   65.80
  44.92   69.74
  49.0    69.74
  54.92   72.07
  58.42   73.58
  61.42   75.39
  66.42   76.98
  70.67   79.89
  74.75   80.98
  80.42   82.20
  82.42   82.57
  84.92   82.74
  93.42   83.41
END


PROCED F100_4
! Data from Fisher et al. (1998)
! Data from procedure F100_4 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=61.8, VFatC=0.33
  SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_4a CVen
  PLOT /DATA=f100_4b CTCOH
  PLOT /DATA=f100_4c CBldTCA
  PLOT /DATA=f100_4d AUrnTCA
  PLOT /DATA=f100_4e AUrnTCOGTCOH
END

DATA F100_4a (T, CVen)
   0.55   0.55
   1.0    0.81
   2.12   1.30
   3.05   1.37
   4.0    1.43
   4.25   0.81
   4.50   0.54
   5.0    0.35
   6.0    0.18
END

DATA F100_4b (T, CTCOH)
   1.0    0.39
   2.12   1.2
   3.05   1.59
   4.0    1.93
   4.25   1.97
   4.50   1.75
   5.0    1.63
   6.0    1.32
   8.05   1.10
  10.08   0.91
  14.03   0.83
  18.02   0.69
  22.02   0.54
END

DATA F100_4c (T, CBldTCA)
   0.55    0.47
   1.0     1.05
   2.12    2.73
   3.05    3.85
   4.0     4.82
   4.25    5.02
   4.50    5.29
   5.0     5.37
   6.0     6.01
   8.05    7.60
  10.08    6.77
  14.03    8.65
  18.02    9.49
  22.02   10.64
  46.08    9.58
  75.67    8.55
  94.25    7.82
END

DATA F100_4d (T, AUrnTCA)
   2.33    0.29
```

```
   4.57      1.62
   5.12      2.09
   6.12      4.01
   8.12      5.81
  10.33      8.27
  12.08     10.21
  14.12     13.06
  16.0      16.29
  18.08     19.09
  20.0      21.96
  21.92     24.17
  25.08     27.09
  29.25     29.05
  32.58     35.13
  35.83     45.84
  38.33     56.12
  41.0      65.21
  45.0      75.98
  48.83     81.05
  50.33     83.74
  53.67     87.89
  56.33     91.72
  59.33     97.13
  66.83    100.34
  73.25    102.88
  80.58    106.50
  83.5     110.02
  86.0     113.61
  93.0     117.51
END

DATA F100_4e (T, AUrnTCOGTCOH)
   2.33     4.52
   4.57     8.37
   5.12    12.49
   6.12    19.46
   8.12    29.26
  10.33    35.93
  12.08    40.21
  14.12    44.90
  16.0     48.15
  18.08    51.04
  20.0     55.72
  21.92    58.76
  25.08    60.75
  29.25    62.24
  32.58    72.07
  35.83    76.15
  38.33    79.24
  41.0     81.48
  45.0     83.84
  48.83    86.37
  50.33    87.44
  53.67    88.84
  56.33    90.90
  59.33    92.91
  66.83    94.07
  73.25    94.96
  80.58    96.17
  83.5     96.82
  86.0     97.41
  93.0     98.54
END
```

```
PROCED F100_5
! Data from Fisher et al. (1998)
! Data from procedure F100_5 (in Bld_F,
Exh_F and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=67.3, VFatC=0.35
  SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_5a CVen
  PLOT /DATA=f100_5b CTCOH
  PLOT /DATA=f100_5c CBldTCA
  PLOT /DATA=f100_5d CAlvPPM
  PLOT /DATA=f100_5e AUrnTCA
  PLOT /DATA=f100_5f AUrnTCOGTCOH
END

DATA F100_5a (T, CVen)
   0.5    0.74
   1.0    1.0
   2.0    1.27
   3.0    1.45
   4.0    1.19
   4.25   0.81
   4.55   0.66
   5.0    0.46
   6.02   0.25
   8.02   0.19
END

DATA F100_5b (T, CTCOH)
   1.0    0.41
   2.0    0.78
   3.0    1.04
   4.0    1.18
   4.25   1.17
   4.55   1.18
   5.0    1.18
   8.02   0.84
  10.0    0.72
  12.0    0.82
  14.0    0.56
  18.02   0.49
  20.0    0.41
END

DATA F100_5c (T, CBldTCA)
   0.5    0.25
   1.0    0.76
   2.0    1.48
   3.0    2.21
   4.0    2.79
   4.25   2.78
   4.55   3.12
   5.0    3.23
   6.02   3.52
   8.02   4.76
  10.0    4.95
```

```
  12.0    5.29
  14.0    5.33
  18.02   6.46
  20.0    6.91
  22.0    7.10
  46.58   6.63
  70.5    5.28
END

DATA F100_5d (T, CAlvPPM)
  4.25   4.243
  4.55   2.798
  5.0    1.849
  6.02   1.467
  8.02   0.681
 10.0    0.452
 12.0    0.409
 14.0    0.356
END

DATA F100_5e (T, AUrnTCA)
  4.67     0.69
  5.0      0.80
  6.3      1.64
  8.08     3.16
 10.08     4.95
 12.07     7.19
 14.08     9.89
 16.12    13.14
 18.11    17.46
 20.1     21.67
 22.12    26.40
 22.67    29.05
 26.5     35.18
 29.67    41.73
 34.17    49.36
 35.67    50.76
 40.67    56.47
 43.67    60.68
 47.17    69.00
 49.67    73.32
 53.42    76.81
 56.17    79.16
 58.0     81.70
 59.67    83.84
 60.17    84.56
 61.67    86.11
 67.67    91.59
 72.67    95.63
 76.67   100.35
 82.67   110.14
 84.17   111.45
 85.67   112.62
 91.67   115.92
END

DATA F100_5f (T, AUrnTCOGTCOH)
  4.67    9.98
  5.0     9.98
  6.3    12.41
  8.08   16.09
 10.08   18.99
 12.07   20.96
 14.08   23.08
 16.12   24.46
 18.11   26.22
 20.1    27.92
 22.12   29.05
 22.67   29.64
 26.5    32.31
 29.67   34.40
 34.17   36.58
 35.67   37.14
 40.67   38.80
 43.67   39.86
 47.17   40.61
 49.67   41.58
 53.42   42.31
 56.17   42.94
 58.0    43.30
 59.67   43.53
 60.17   43.60
 61.67   43.78
 67.67   44.79
 72.67   45.19
 76.67   45.69
 82.67   46.42
 84.17   46.54
 85.67   46.60
 91.67   47.13
END


PROCED F100_6Param
  SET VMaxC=3.0
END

PROCED F100_6
! Data from Fisher et al. (1998)
! Data from procedure F100_6 (in Bld_F,
Exh_F and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  F100_6Param
  SET BW=62.3, VFatC=0.24
  SET Conc=97.7, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
  START /NC
  PLOT /DATA=f100_6a CVen
  PLOT /DATA=f100_6b CTCOH
  PLOT /DATA=f100_6c CBldTCA
  PLOT /DATA=f100_6d CAlvPPM
  PLOT /DATA=f100_6e CDCA
  PLOT /DATA=f100_6f AUrnTCA
  PLOT /DATA=f100_6g AUrnTCOGTCOH
END

DATA F100_6a (T, CVen)
  0.5    0.83
  1.0    0.99
  2.03   1.20
  3.0    1.59
  4.03   2.03
  4.25   1.33
  4.5    0.87
```

```
     5.0    0.42
     6.0    0.21
     8.0    0.22
    10.0    0.15
END

DATA F100_6b (T, CTCOH)
     2.03   0.53
     3.0    0.83
     4.03   1.27
     4.25   0.92
     4.5    0.85
     5.0    1.17
     6.0    1.03
     8.0    0.86
    10.0    0.80
    12.0    0.71
    14.03   0.62
    16.03   0.55
    18.07   0.48
    20.0    0.41
END

DATA F100_6c (T, CBldTCA)
     0.5    0.44
     1.0    0.97
     2.03   2.16
     3.0    3.79
     4.03   5.12
     4.25   5.35
     4.5    5.60
     5.0    5.88
     6.0    6.55
     8.0    7.30
    10.0    7.66
    12.0    8.61
    14.03   8.73
    16.03   9.65
    18.07   8.29
    20.0    8.60
    22.0   10.2
    47.95   6.15
    71.98   7.11
   101.22   6.73
END

DATA F100_6d (T, CAlvPPM)
     4.03  22.398
     4.25   7.317
     4.5    5.917
     5.0    2.903
     6.0    1.382
     8.0    0.982
    10.0    0.691
    12.0    0.524
    14.03   0.428
END

DATA F100_6e (T, CDCA)
     1.0    0.005
     2.03   0.014
     3.0    0.005
END

DATA F100_6f (T, AUrnTCA)
     4.55    0.30
     5.12    0.56
     6.08    1.75
     8.19    1.97
    10.19    3.75
    12.17    6.58
    14.33    6.81
    16.23    8.64
    18.19   10.30
    20.13   12.13
    22.38   13.64
    31.92   15.77
    34.25   18.03
    36.92   18.16
    48.67   22.69
    55.83   28.52
    59.0    30.85
    63.5    31.36
    70.8    33.88
    76.0    37.20
    85.5    41.32
    87.25   42.86
    88.08   49.42
    94.75   54.14
END

DATA F100_6g (T, AUrnTCOGTCOH)
     4.55   11.67
     5.12   14.56
     6.08   20.78
     8.19   25.55
    10.19   34.83
    12.17   45.33
    14.33   45.98
    16.23   54.21
    18.19   60.91
    20.13   68.01
    22.38   73.35
    31.92   75.14
    34.25   79.52
    36.92   79.97
    48.67   85.95
    55.83   90.84
    59.0    91.82
    63.5    92.13
    70.8    92.13
    76.0    95.09
    85.5    96.05
    87.25   96.34
    88.08   96.45
    94.75   97.45
END

PROCED F100_7
! Data from Fisher et al. (1998)
! Data from procedure F100_7 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
```

```
  SET BW=63.2, VFatC=0.26
  SET Conc=101.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=f100_7a CVen
  PLOT /DATA=f100_7b CTCOH
  PLOT /DATA=f100_7c CBldTCA
  PLOT /DATA=f100_7d AUrnTCA
  PLOT /DATA=f100_7e AUrnTCOGTCOH
END

DATA F100_7a (T, CVen)
   0.52   0.53
   1.0    1.0
   2.0    0.97
   3.0    1.31
   4.0    1.48
   4.28   0.84
   4.5    0.58
   5.0    0.39
END

DATA F100_7b (T, CTCOH)
   0.52   0.35
   1.0    0.58
   2.0    0.86
   3.0    1.60
   4.0    2.03
   4.28   2.04
   4.5    1.93
   5.0    1.95
   6.05   1.79
   8.0    1.29
  10.0    1.14
  12.0    1.03
END

DATA F100_7c (T, CBldTCA)
   0.52   0.39
   1.0    1.08
   2.0    1.90
   3.0    3.83
   4.0    4.48
   4.28   4.65
   4.5    4.80
   5.0    4.73
   6.05   6.02
   8.0    6.02
  10.0    7.12
  12.0    7.13
  46.75   9.10
  73.97   6.92
  95.42   6.14
END

DATA F100_7d (T, AUrnTCA)
   4.67     2.51
   5.17     3.07
   6.25     6.21
   8.08     9.97
  10.13    13.01
  12.08    16.35
  14.12    20.65
  16.02    23.23
  18.02    26.31
  20.17    26.31
  25.27    34.28
  25.75    34.84
  30.0     42.19
  34.5     51.62
  37.92    61.19
  45.08    75.52
  49.33    81.43
  56.92    92.21
  60.42   104.12
  68.33   116.32
  72.58   121.17
  80.5    131.94
  84.33   134.71
  86.17   136.09
  93.5    142.30
END

DATA F100_7e (T, AUrnTCOGTCOH)
   4.67    37.76
   5.17    42.18
   6.25    48.68
   8.08    60.91
  10.13    72.32
  12.08    81.05
  14.12    86.76
  16.02    94.78
  18.02   100.92
  20.17   105.91
  25.27   115.12
  25.75   116.22
  30.0    125.29
  34.5    131.36
  37.92   135.91
  45.08   143.62
  49.33   146.34
  56.92   149.70
  60.42   151.17
  68.33   153.38
  72.58   154.28
  80.5    155.70
  84.33   155.93
  86.17   156.09
  93.5    156.70
END


PROCED F100_8
! Data from Fisher et al. (1998)
! Data from procedure F100_8 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=48.6, VFatC=0.23
  SET Conc=103.3, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
  START /NC
  PLOT /DATA=f100_8a CVen
```

```
  PLOT /DATA=f100_8b CTCOH
  PLOT /DATA=f100_8c CBldTCA
  PLOT /DATA=f100_8d CDCA
  PLOT /DATA=f100_8e AUrnTCA
  PLOT /DATA=f100_8f AUrnTCOGTCOH
END

DATA F100_8a (T, CVen)
    0.5     1.32
    1.0     1.68
    2.0     1.86
    3.0     2.37
    4.0     2.66
    4.25    2.10
    4.5     1.23
    5.0     0.83
    6.0     0.42
    8.05    0.33
   10.03    0.30
END

DATA F100_8b (T, CTCOH)
    0.5     0.47
    1.0     0.68
    2.0     1.51
    3.0     2.15
    4.0     2.72
    4.25    2.87
    4.5     2.77
    5.0     2.63
    6.0     2.30
    8.05    1.90
   10.03    1.59
   12.05    1.28
   14.02    1.23
   16.0     1.10
   18.0     0.98
   20.0     0.72
   22.0     0.71
END

DATA F100_8c (T, CBldTCA)
    0.5     0.27
    1.0     0.70
    2.0     1.48
    3.0     2.80
    4.0     3.92
    4.25    3.86
    4.5     3.98
    5.0     4.55
    6.0     4.80
    8.05    5.96
   10.03    6.09
   12.05    6.41
   14.02    7.01
   16.0     7.23
   18.0     7.57
   20.0     7.68
   22.0     8.46
   45.03    8.75
   69.03    7.73
   93.13    5.72
  264.0     0.53
END

DATA F100_8d (T, CDCA)
    0.5     0.008
    1.0     0.008
    2.0     0.007
    3.0     0.007
    4.0     0.006
    4.25    0.009
    4.5     0.013
    5.0     0.012
    6.0     0.011
    8.05    0.005
   12.05    0.005
   16.0     0.004
   18.0     0.004
   22.0     0.005
   45.03    0.006
   69.03    0.004
END

DATA F100_8e (T, AUrnTCA)
    4.58      2.34
    5.05      2.92
    6.05      5.27
    8.08      8.33
   10.07     12.15
   12.08     17.02
   14.31     21.46
   16.05     26.02
   18.05     28.88
   20.03     32.60
   22.08     37.96
   43.33     80.45
   45.58     85.25
   47.58     87.93
   49.17     91.55
   53.58     99.63
   61.33    110.21
   67.33    114.43
   70.58    118.52
   74.58    123.23
   77.25    128.78
   83.25    133.51
   84.25    134.95
   85.17    136.29
   90.5     143.83
END

DATA F100_8f (T, AUrnTCOGTCOH)
    4.58     15.54
    5.05     18.22
    6.05     24.58
    8.08     33.76
   10.07     41.25
   12.08     47.80
   14.31     54.36
   16.05     59.99
   18.05     63.23
   20.03     68.23
   22.08     73.90
   43.33    110.18
   45.58    112.61
```

```
  47.58   113.70
  49.17   115.14
  53.58   118.20
  61.33   122.07
  67.33   124.30
  70.58   125.29
  74.58   126.29
  77.25   127.48
  83.25   128.07
  84.25   128.31
  85.17   128.49
  90.5    129.56
END


PROCED MaleHiM
! Data from Fisher et al. (1998)
! M file created Tue 18 Nov 2003
! Malehi.m
! Last Modified:  22 Jan 2004
! Modified by: Deborah Keys
! 100ppm 4 hr inhalation blood:
fish,mahle,abbas

!  Male
  Human
  ResetDoses
  SET BW=60.9, VFatC=0.10
  SET Conc=101.1, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
  START /NC
  PLOT /DATA=male100_7a CTCOH
  PLOT /DATA=male100_7b CBldTCA
  PLOT /DATA=male100_7c AUrnTCA
  PLOT /DATA=male100_7d AUrnTCOGTCOH
END

DATA Male100_7a (T, CTCOH)
    0.5    0.28
    1.0    0.76
    2.0    1.92
    3.0    1.69
    4.0    2.34
    4.3    2.34
    4.5    2.16
    5.0    2.13
    6.0    1.95
    8.0    1.61
   10.0    1.33
   12.0    1.58
   14.0    0.84
   16.0    0.77
   18.0    0.57
   20.03   0.76
END

DATA Male100_7b (T, CBldTCA)
    0.5    0.36
    1.0    0.84
    2.0    1.73
    3.0    2.6
    4.0    3.42
```

```
    4.3     3.9
    4.5     3.67
    5.0     4.47
    6.0     5.0
    8.0     5.95
   10.0     6.74
   12.0     7.12
   14.0     7.75
   16.0     8.22
   18.0     8.17
   20.03    9.01
   49.75   10.66
   73.8     8.6
   95.24    7.46
  264.0     3.13
END

DATA Male100_7c (T, AUrnTCA)
    4.75    0.93
    7.95    3.02
   14.08    5.95
   16.08    7.07
   18.1     8.28
   20.25    9.63
   24.67   13.46
   29.17   15.73
   32.67   20.11
   35.33   22.71
   38.83   24.07
   44.25   25.6
   49.67   27.51
   55.92   29.6
   58.75   33.36
   68.25   39.61
   73.83   43.7
   75.92   45.78
   77.92   48.52
   81.17   51.21
   82.58   53.54
   92.17   60.72
END

DATA Male100_7d (T, AUrnTCOGTCOH)
    4.75    40.71
    7.95    69.81
   14.08    89.76
   16.08    96.8
   18.1    102.69
   20.25   107.93
   24.67   121.3
   29.17   128.51
   32.67   135.51
   35.33   138.05
   38.83   140.2
   44.25   142.48
   49.67   144.47
   55.92   144.96
   58.75   145.55
   68.25   146.67
   73.83   147.09
   75.92   147.25
   77.92   147.38
   81.17   147.5
```

```
   82.58   147.62
   92.17   147.98
END


PROCED MaleLoM
! Data from Fisher et al. (1998)
! M file created Tue 18 Nov 2003
! Malelo.m
! Last Modified:  22 Jan 2004
! Modified by: Deborah Keys
! 100ppm 4 hr inhalation blood:
fish,mahle,abbas

!  Male
  Human
  ResetDoses
  SET BW=82.7, VFatC=0.14
  SET Conc=102.6, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC
  PLOT /DATA=male100_3a CTCOH
  PLOT /DATA=male100_3b CBldTCA
  PLOT /DATA=male100_3c AUrnTCA
  PLOT /DATA=male100_3d AUrnTCOGTCOH
END

DATA Male100_3a (T, CTCOH)
   0.5    0.45
   1.07   0.77
   2.0    1.51
   3.0    2.41
   3.98   3.3
   4.25   3.64
   4.5    3.67
   5.0    3.48
   6.0    3.05
   8.0    2.52
  10.02   2.38
  12.0    2.16
  14.0    1.73
  16.02   1.48
  18.07   1.12
  20.0    1.01
  22.0    0.85
END

DATA Male100_3b (T, CBldTCA)
   0.5    0.23
   1.07   0.49
   2.0    1.07
   3.0    1.89
   3.98   2.87
   4.25   3.69
   4.5    3.87
   5.0    3.59
   6.0    4.18
   8.0    4.71
  10.02   5.46
  12.0    5.67
  14.0    5.97
  16.02   6.05
  18.07   6.22
  20.0    7.54
  22.0    7.26
  46.85   8.43
  71.47   3.86
  95.5    3.55
END

DATA Male100_3c (T, AUrnTCA)
   3.03    0.488
   4.75    0.961
   6.7     2.09
   8.25    2.96
  10.17    5.56
  12.08    7.17
  14.19    8.37
  15.58    9.09
  17.6     9.7
  18.23   10.13
  19.58   10.99
  20.05   11.24
  21.33   11.88
  22.17   12.36
  23.2    13.03
  35.42   14.18
  40.67   16.14
  46.67   18.07
  47.17   19.06
  52.33   20.35
  55.25   23.68
  68.17   24.71
  69.75   27.02
END

DATA Male100_3d (T, AUrnTCOGTCOH)
   3.03    32.7
   4.75    60.26
   6.7     97.98
   8.25   130.67
  10.17   182.9
  12.08   204.64
  14.19   224.53
  15.58   233.79
  17.6    240.99
  18.23   245.36
  19.58   253.46
  20.05   255.9
  21.33   261.17
  22.17   265.4
  23.2    269.76
  35.42   271.64
  40.67   276.15
  46.67   277.54
  47.17   277.83
  52.33   278.12
  55.25   278.81
  68.17   278.88
  69.75   279.07
END


SET CMD=5
```